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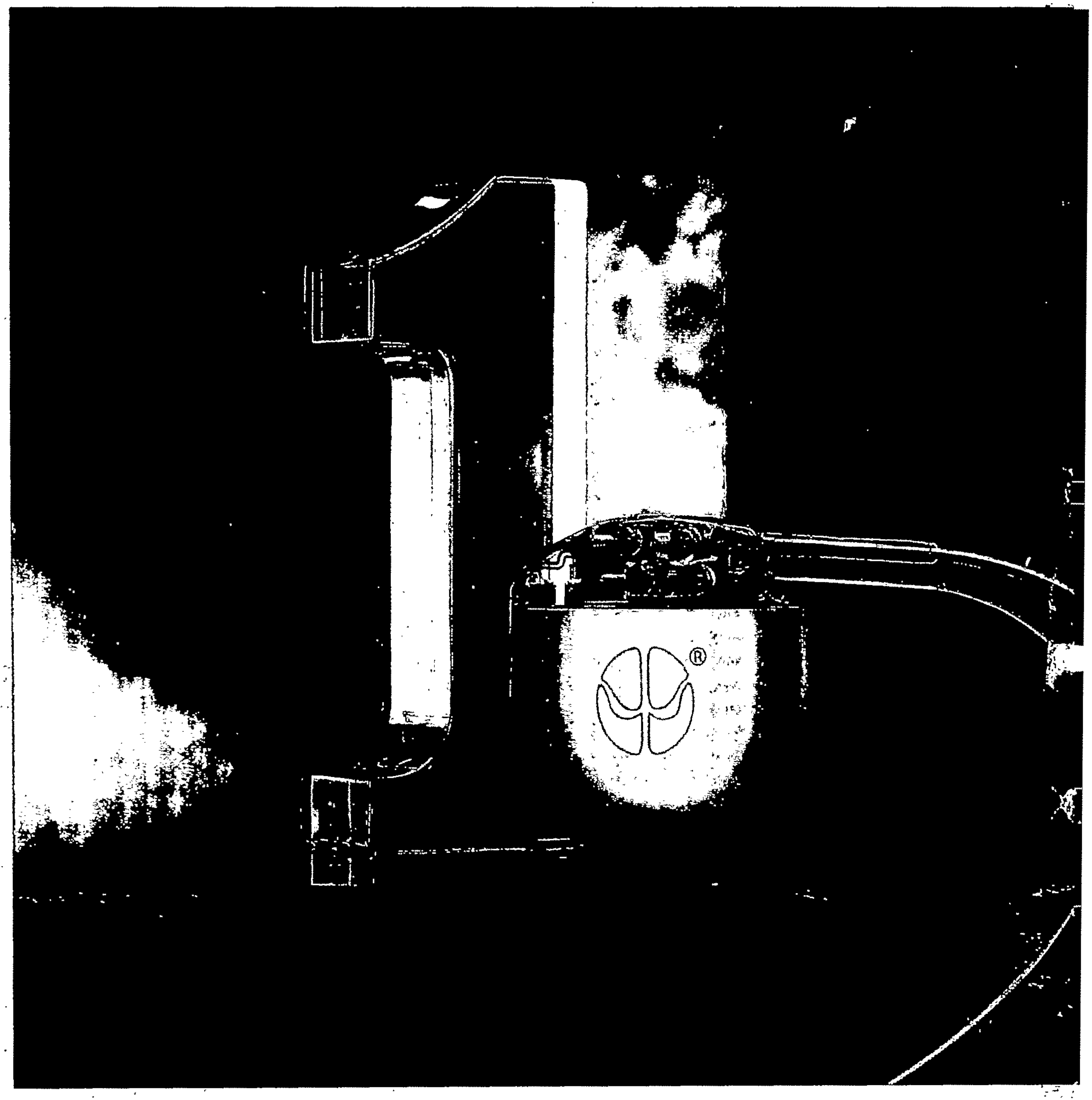

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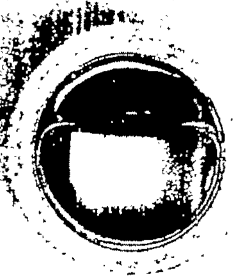
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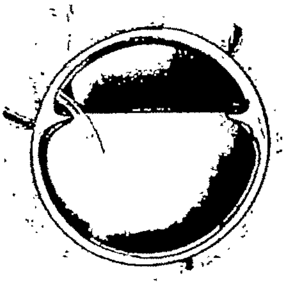
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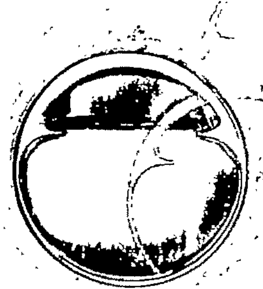
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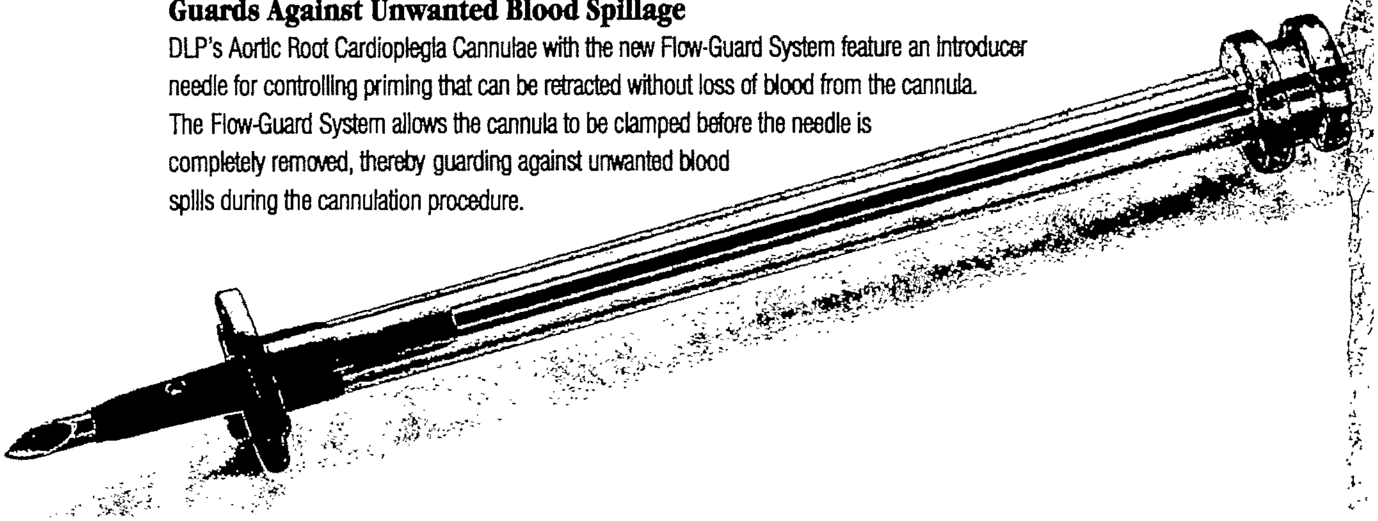

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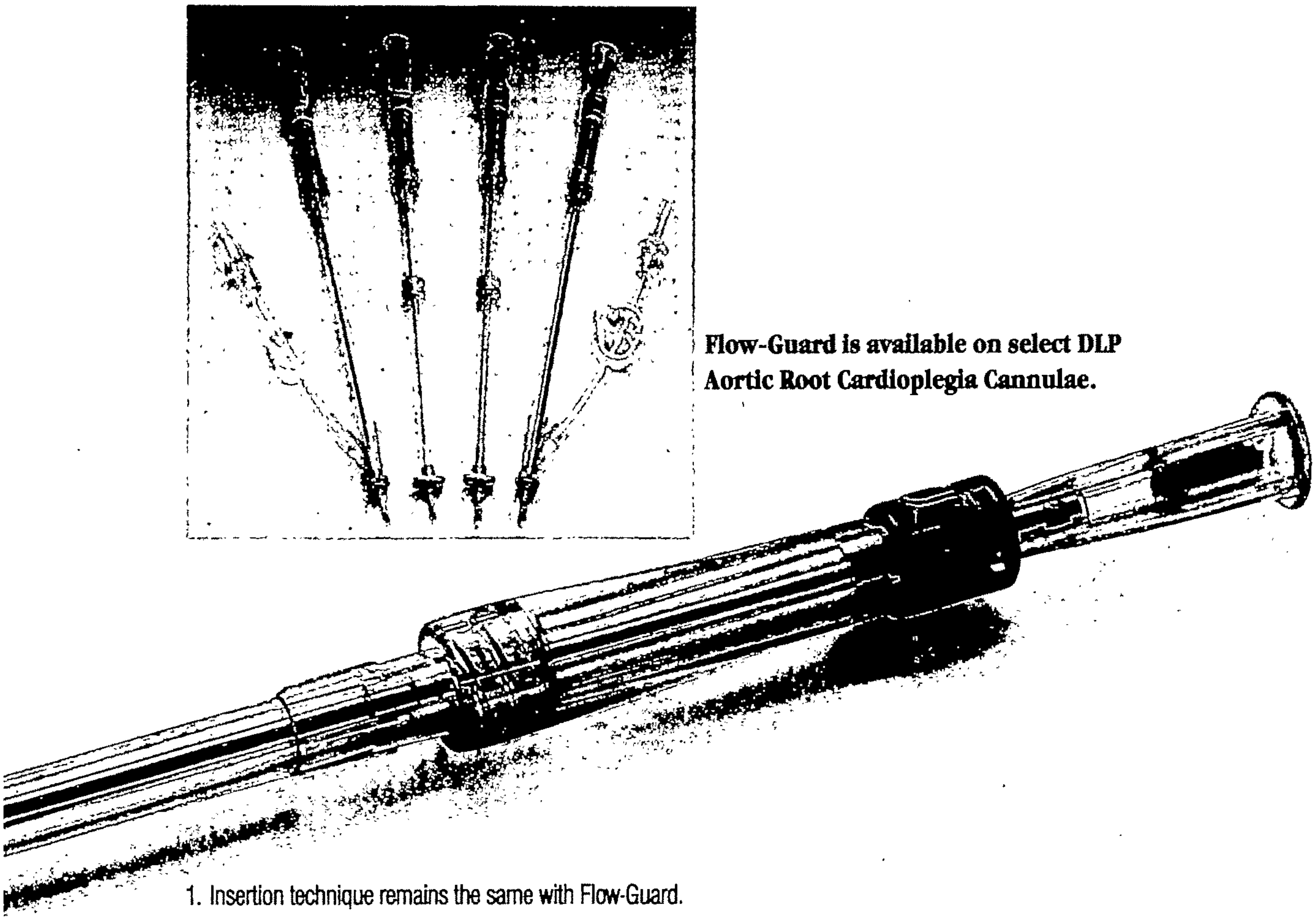

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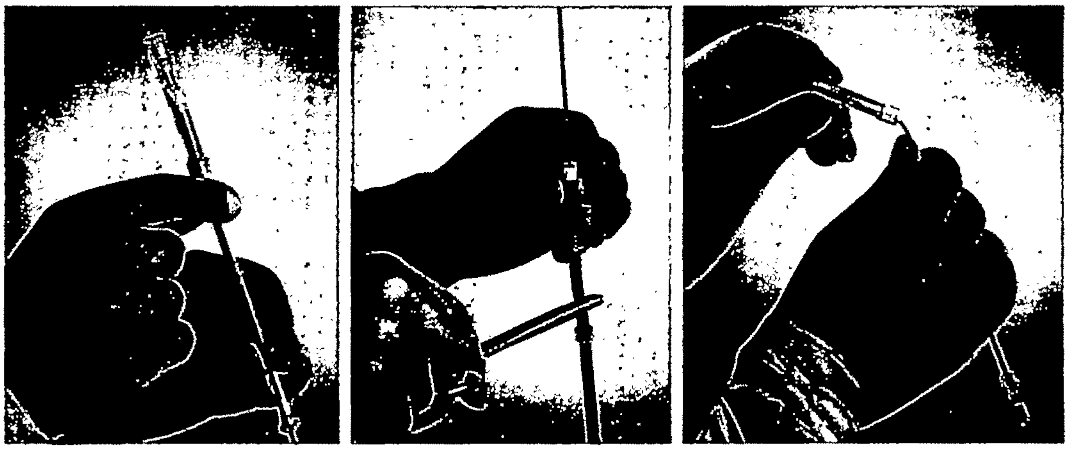

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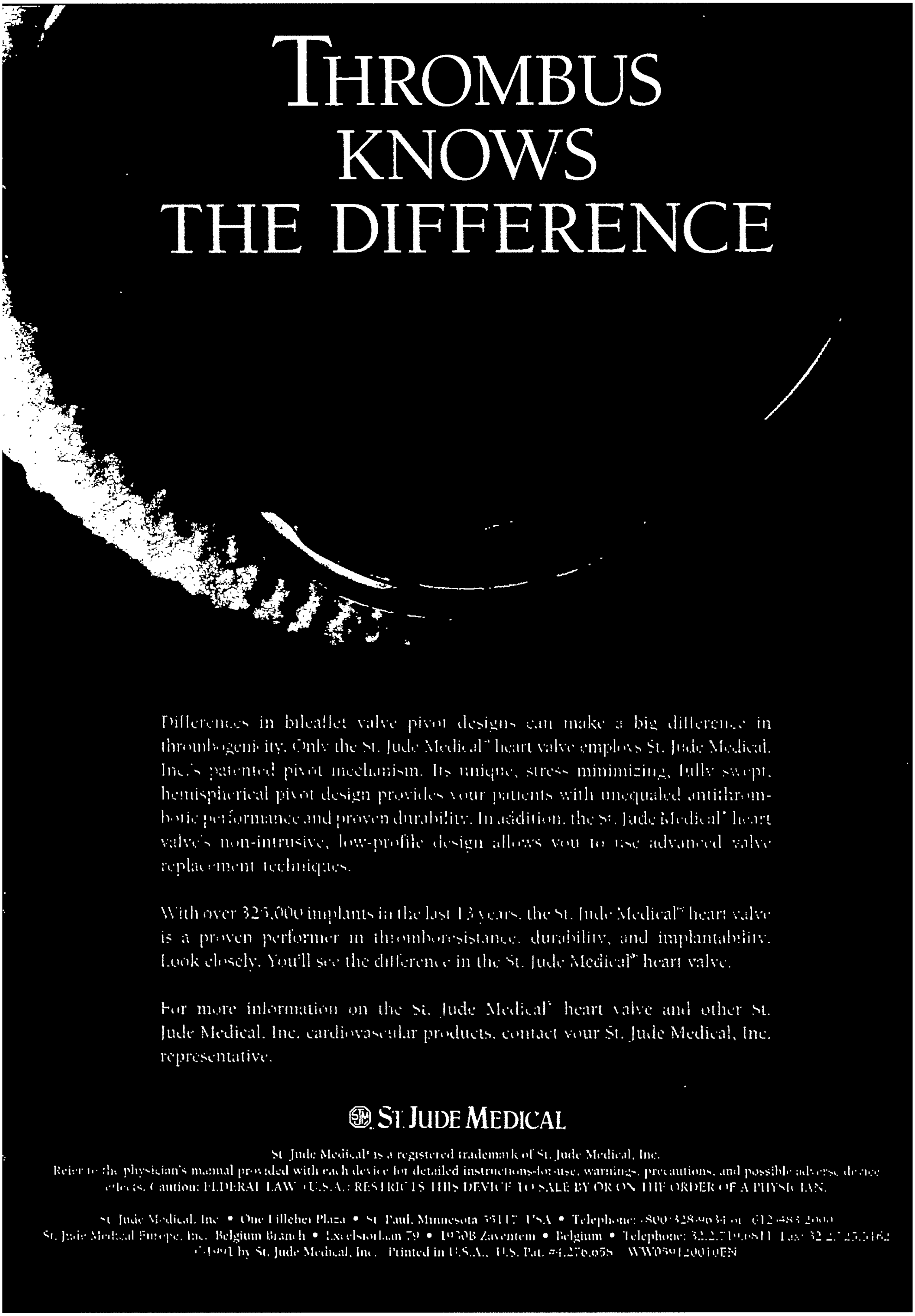

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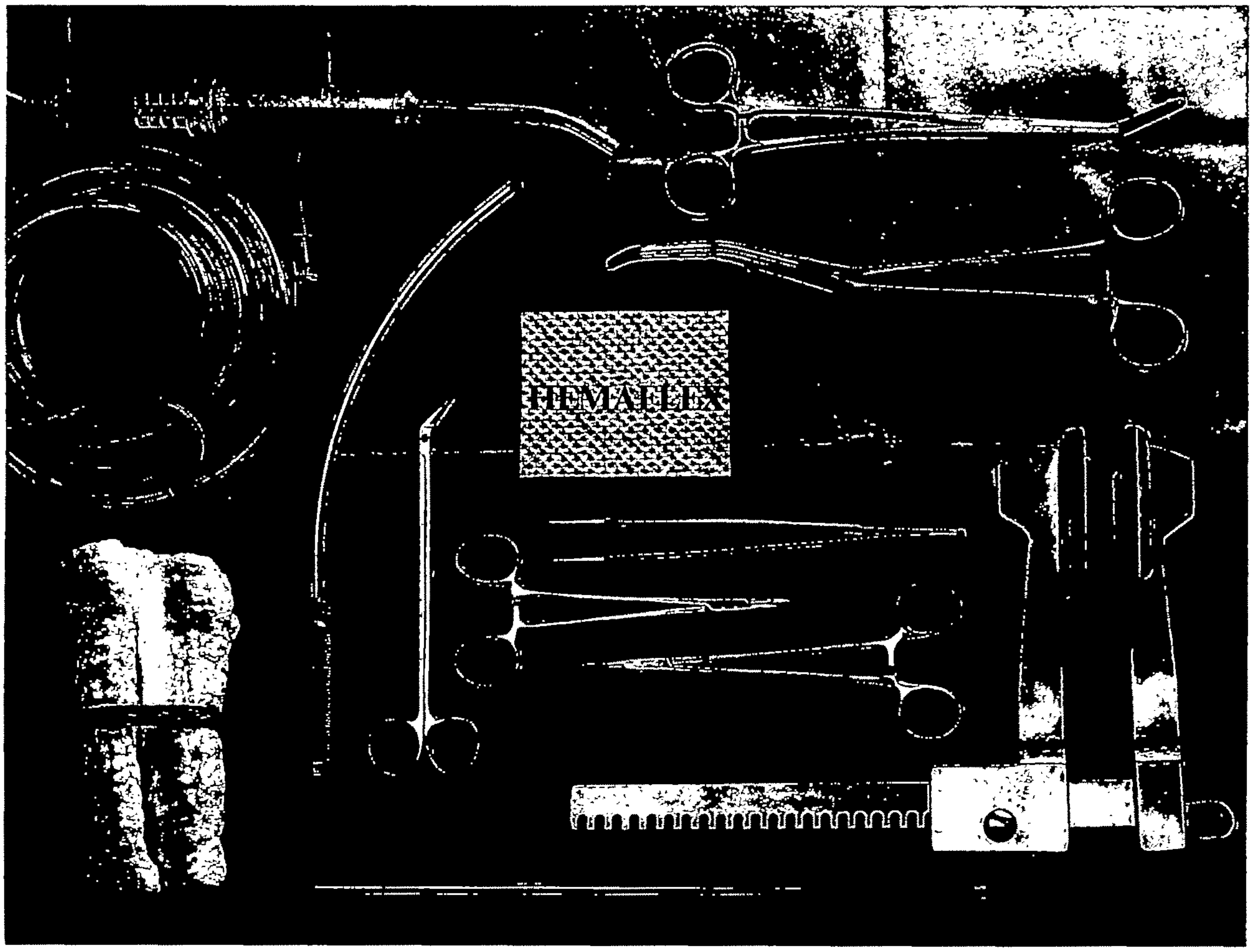

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Design

As compared to other types of prostheses, preserved porcine bioprostheses exhibit certain potential advantages: the need for long-term anticoagulation may be minimized; and although the durability of porcine bioprostheses is a limiting factor in long-term evaluation, tissue degradation is usually progressive and symptomatic, thereby permitting detection with proper annual follow-up in person with a physician, and elective intervention when necessary.

Models 6625LP and 6625-ESR-LP Mitral Carpentier-Edwards® Duraflex™ Bioprostheses are comprised of porcine aortic valves that have been preserved in buffered glutaraldehyde and then mounted on flexible frames. Glutaraldehyde is shown to both reduce the antigenicity of porcine xenograft valves and increase tissue stability.

The frame is designed to be flexible at the orifice as well as at the commissures. The compliance of the stent's commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The flexibility of the orifice is intended to reduce the loading shock at the base of the leaflet. The flexible orifice concept is based on the physiology and mechanics of natural heart valves and reported experience with implantation of unstented homografts.

The lightweight frame is made of Elgiloy,** a corrosion-resistant alloy, chosen because of its superior spring efficiency and fatigue-resistant characteristics.

The metal frame is covered with a porous, knitted polytetrafluoroethylene cloth to facilitate tissue ingrowth and encapsulation. The inflow orifice is contoured to support the right coronary cusp of the porcine valve. The commissure supports are not equidistant to conform to the anatomical configuration of the porcine aortic valve. The suture ring has a soft, silicone-rubber insert that is covered with a porous, seamless polytetrafluoroethylene cloth. The compliant nature of the suture ring facilitates coaptation between the valve and an often irregular or calcific tissue bed.

The porcine aortic valves are fixed in buffered glutaraldehyde, and then mounted on cloth-covered frames. After mounting, the valves are tested in vitro to ascertain their competency and flow characteristics. After final inspection, the valves are sterilized, rinsed, and then transferred into fresh glutaraldehyde and packaged under aseptic conditions.

Low Pressure Fixation

In vitro studies by Broom, et al, advise that to maintain optimum mechanical properties in the fixed porcine aortic leaflet tissue, the full collagen waveform or crimp-originally present in the relaxed fresh tissue should be retained. In addition, these studies show that the collagen waveform is sensitive to alteration at fixation pressures as low as 4 mm Hg. Edwards CVS Division has developed a process to fix porcine aortic valves at a hydrostatic pressure less than 4 mm Hg to minimize alterations in the collagen waveform of the aortic valve tissue. Low pressure fixation of Carpentier-Edwards Duraflex™ bioprostheses is intended to increase the clinical durability of these valves; however, data regarding Carpentier-Edwards Duraflex™ bioprostheses are insufficient to demonstrate that durability has been increased by this preparation technique or that calcification has been reduced.

Indications

Bioprostheses are indicated for use in patients suffering from valvular heart disease. Mitral valvular heart disease is a condition involving any of the following: obstruction of the heart valve or stenosis; leakage of the valve, known as regurgitation or insufficiency; and combination of the two, sometimes referred to as mixed disease or combined lesions.

Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease, and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia.

Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards Duraflex™ bioprosthesis is intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on maintenance hemodialysis.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after carefully evaluating the short- and long-term risks and benefits to the patient, and considering alternative methods of treatment. The overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of tissue valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (See Clinical Experience).

Careful and continuous medical follow-up (at least annually by a visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. Please refer to the most recent Clinical Experience attachment for data on anticoagulation relating to these valves. The appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards Duraflex™ bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across Carpentier-Edwards® Duraflex™ bioprostheses could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in a sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C (50°F) and 25°C (77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact with the eyes, seek medical attention.

Surgical Precautions

The models 6625LP and 6625-ESR-LP Duraflex™ mitral valves are unapproved for indications other than mitral valve replacement.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards Duraflex™ bioprostheses, compiled from the literature and from reports received through the complaint handling system in accordance with the United States (federal) regulations establishing Good Manufacturing Practices section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period, and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards Duraflex™ bioprostheses to calcification as compared to other commercially available porcine valves.

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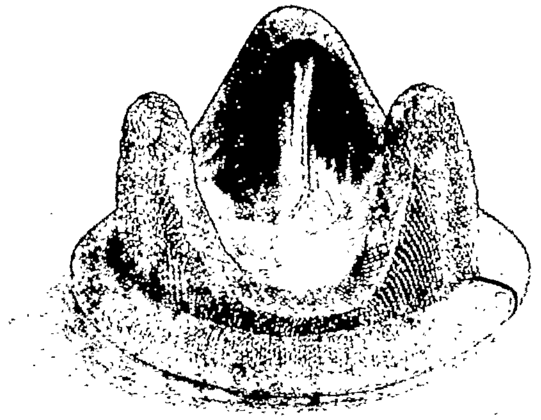

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You're on bypass and the power fails . . .

Photo by Kip Seymour. © 1988 Fairfax Hospital

When power fails, protection of arterial flow becomes the first priority. For many perfusionists that means resorting to a mechanical hand crank. But what happens to the remaining pumps? Or to your safety and monitoring equipment?

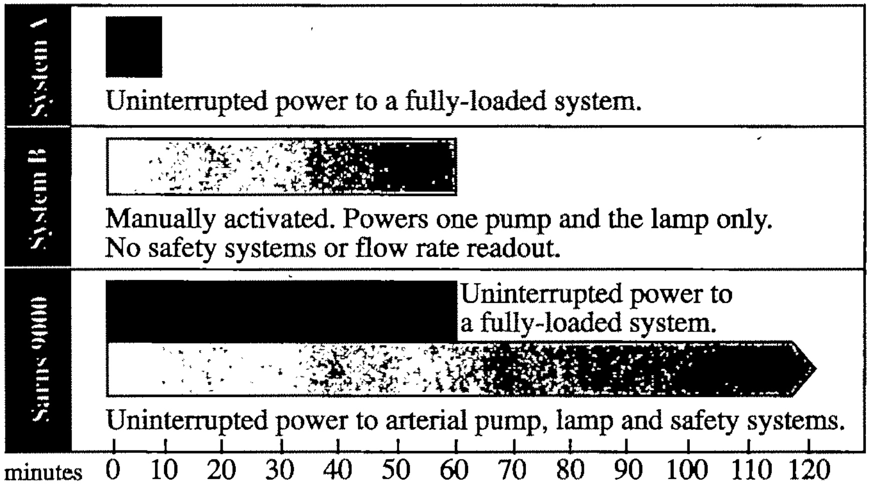
Worse still, back-up generators fail.[1]

In a survey conducted by Kurusz and associates,[2] electrical failure ranked as the fourth most frequent perfusion accident. Among the 608 respondents, electrical failure during CPB was reported by 42.3%.

When power fails, protection of arterial flow becomes first priority. That's why battery back-up with the Sarns™ 9000 perfusion system is immediate and automatic. That's why power supplies for pumps and monitoring functions are effectively isolated, and backed up by a third power source. And why critical pumping and safety systems continue to operate.

Fundamental safety systems built into the Sarns 9000 perfusion system help ensure that arterial flow, adequate oxygenation and air detection continue even if external power stops.

Back-up battery duration



Automatic battery back-up supplies uninterrupted power to the entire Sarns 9000 perfusion system for at least 60 minutes, or to one pump with safety systems and the lamp for over 2 hours. Yes, there's a hand crank too... just in case.

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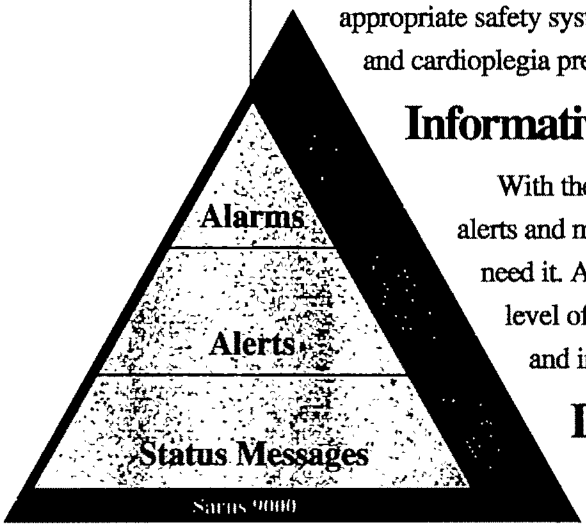
No perfusion system is complete without the constant vigilance and clinical judgment of a well trained perfusionist. The Sarns 9000 system is designed to work with you in guarding patient safety. Designating a pump for arterial perfusion, pulsatile pumping or cardioplegia delivery activates appropriate safety systems—to enforce operator-set limits for arterial and cardioplegia pressures, and to display corresponding patient data.



The Sarns 9000 perfusion system is designed to safeguard your patients with safety systems that complement a perfusionist's constant vigilance and clinical judgment.

Informative alerts and alarms

With the Sarns 9000 system a logical hierarchy of alarms, alerts and messages supplies accurate information when you need it. As the severity of a condition increases, so does the level of visual and audio warning—giving you the time and information necessary to respond appropriately.

Designing for safety

In deference to the demanding clinical setting and the possibility of error,[3] Sarns strives to match technology to function for optimal perfusion. Ergonomic control panels, developed in conjunction with perfusionists, are logically positioned and easy to interpret. They are also intentional, with dual control switches that must be pushed simultaneously to ensure deliberate activation.

A philosophy of safety

Safety consists of more than products—such as air and level detectors—designed specifically to make perfusion safer. It incorporates training and perfusion protocols[4] that affect the safe use of a product. But, most importantly, safety involves the optimal interaction of the perfusionist with the perfusion system. Which is why Sarns philosophy of safety couldn't possibly work without you.

For more information about Sarns systems for safety, call **800/521-2818.** Or write Sarns, 3M Health Care, 6200 Jackson Road, Ann Arbor, MI 48103.

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Footnotes

[1] Greenhalgh D, Thomas W. Blackout during cardiopulmonary bypass. *Anaesthesia.* 1990;45:175. This article reports on power failure accompanied by back-up generator failure.

[2] Kurusz M, Conti VR, Arens JF, et al. Perfusion accident survey. *Proc Amer Acad Cardio Perfusion.* 1986;7:57–65.

[3] Human factors issues with surgical devices. *Tech for Perfusion.* 1991;3:1.

[4] Schabel RK, Berryessa RG, Justison GA, et al. Ten common perfusion problems: Prevention and treatment protocols. *J Extra-Corpor Tech.* 1987;19:392–398. These authors identify the perfusion problems "most likely" to occur, recommend preventive measures, and give examples of emergency protocols.

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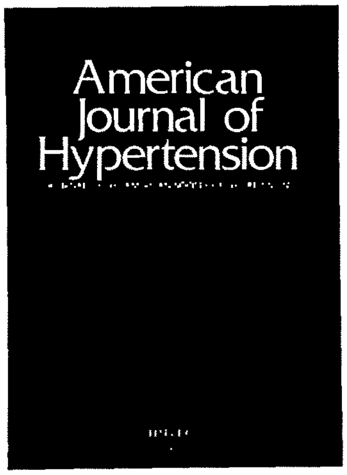

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Carpentier-Edwards®
Pericardial Bioprosthesis
Model 2700 Aortic
For single use only
Indications

Pericardial valves are indicated for use in patients suffering from valvular heart disease. Aortic valvular heart disease is a condition involving any of the following: obstruction of the aortic heart valve or stenosis; leakage of the aortic valve, known as regurgitation, incompetence, or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions.

Aortic valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, and rheumatic heart disease.

Pericardial valves are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards® pericardial valve is intended for use in patients whose aortic valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic valve prosthesis that is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium-metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on a maintenance hemodialysis. Clinical data which establishes the safety and efficacy of the valve for use in patients under the age of 20 is not available; therefore, we recommend careful consideration of its use in younger patients.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment. Overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to the replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis.

Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except where contraindicated) during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall, or history of previous atrial thrombus. However, the appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards® pericardial valves must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards® pericardial valve could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in the sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C and 25°C (50-77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with the eyes, seek medical attention. For more information about glutaraldehyde exposure refer to MSDS BAX 10424, available from Edwards CVS Division.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days), necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards® bioprostheses compiled from the literature and from reports received through the complaint handling system in accordance with the United States (Federal) regulations establishing Good Manufacturing Practices, Section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, and malfunctions of the valve due to distortion at implant, fracture of the Elgiloy wireform, or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and leaflet detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards® pericardial bioprostheses to calcification as compared to commercially available bioprostheses.

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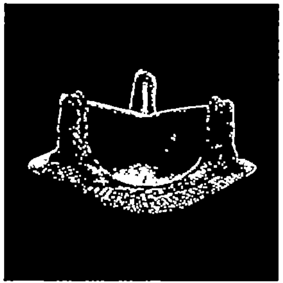

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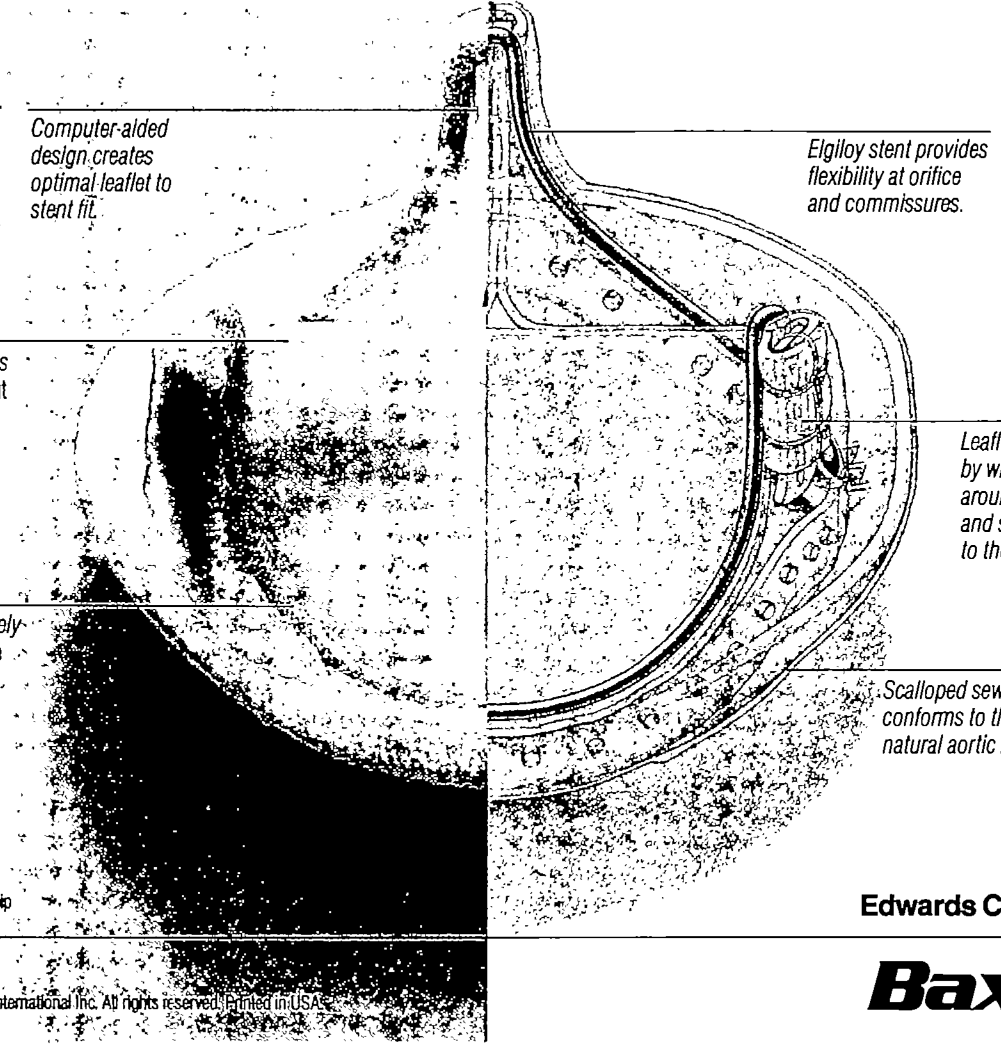
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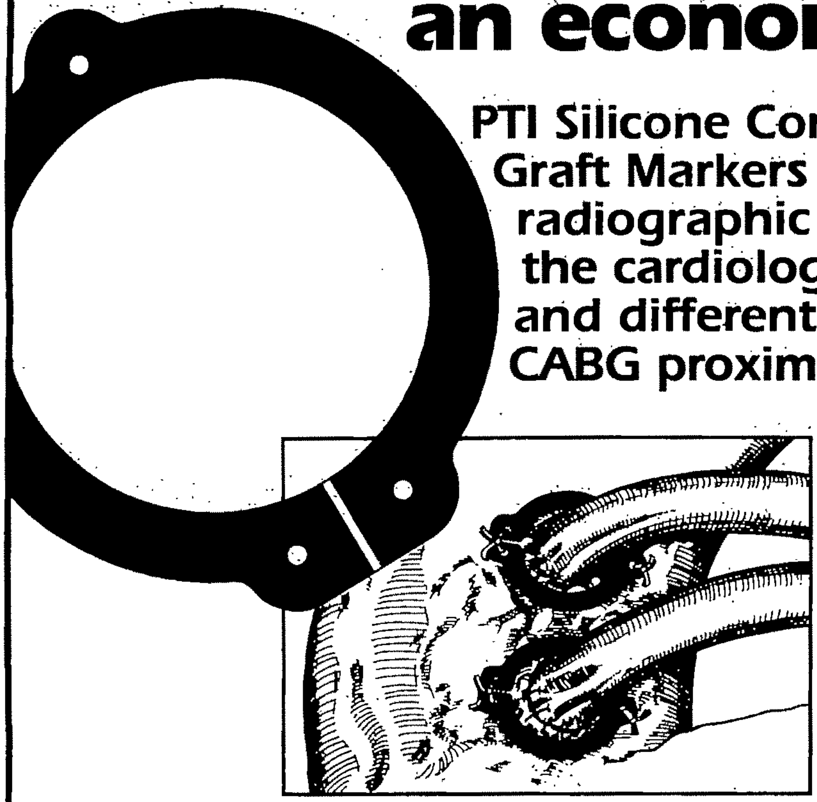

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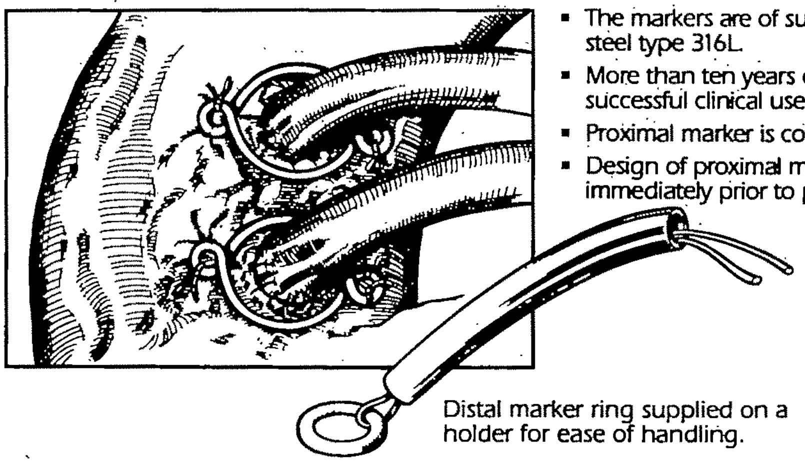

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Forthcoming Articles

Original Articles

Availability of the In Situ Right Gastroepiploic Artery for Coronary Artery Bypass
Tsutomu Saito, MD, Hisayoshi Suma, MD, Yasushi Terada, MD, Yasuhiko Wanibuchi, MD, Sachito Fukuda, MD, and Shoichi Furuta, MD

Blunt Injuries of the Thoracic Aorta
Alan D. Hilgenberg, MD, Diana L. Logan, RN, Cary W. Akins, MD, Mortimer J. Buckley, MD, Willard M. Daggett, MD, Gus J. Vlahakes, MD, and David F. Torchiana, MD

Calcification of Porcine Valves: A Successful New Method of Antimineralization
John Parker Gott, MD, Pan-Chih, MD, Lynne M. A. Dorsey, BS, MBA, John L. Jay, MD, G. Kimble Jett, MD, Frederick J. Schoen, MD, PhD, Robert A. Guyton, MD, and Jean-Marie Girardot, PhD

Chest Wall Stabilization With Synthetic Reabsorbable Material
Francesco Puma, MD, Mark Ragusa, MD, and Giuliano Daddi, MD

Coronary Artery Endothelial Cell and Smooth Muscle Dysfunction After Global Myocardial Ischemia
Rebecca J. Dignan, MD, Cornelius M. Dyke, MD, Anwar S. Abd-Elfattah, PhD, Harry Lutz, PhD, Thomas Yeh, Jr, MD, K. Francis Lee, MD, Jitendra Parmar, MD, and Andrew S. Wechsler, MD

Early Experience With Adult Extracorporeal Membrane Oxygenation in the Modern Era
Harry L. Anderson III, MD, Ralph E. Delius, MD, James M. Sinard, MD, Kenneth R. McCurry, MD, Charles J. Shanley, MD, Robin A. Chapman, RN, Michael B. Shapiro, MD, Jorge L. Rodriguez, MD, and Robert H. Bartlett, MD

Experience With the Symbion Total Artificial Heart as a Bridge to Transplantation
Robert W. Emery, MD, Lyle D. Joyce, MD, Mikel Prieto, MD, Kristen Johnson, RN, Irvin F. Goldenberg, MD, and Marc R. Pritzker, MD

Heart, Heart-Lung, and Lung Transplantation in the First Year of Life
Vaughn A. Starnes, MD, Philip E. Oyer, MD, PhD, Daniel Bernstein, MD, David Baum, MD, Patricia Gamberg, RN, Joan Miller, RN, and Norman E. Shumway, MD, PhD

Platelet-Leukocyte Plasmapheresis Attenuates the Deleterious Effects of Cardiopulmonary Bypass
Gerald G. Davies, MD, Douglas G. Wells, MD, Thomas M. Mabee, MD, Richard Sadler, MD, and Nicholas J. Melling, PA

Selective Surgical Approach for Atrioventricular Reentrant Tachycardia
Alexander S. Geha, MD, Lee A. Biblo, MD, Mark D. Carlson, MD, and Albert L. Waldo, MD

Case Reports

Prolonged Intraaortic Balloon Support for Septal Rupture After Myocardial Infarction
Tulio Estrada-Quintero, MD, Barry F. Uretsky, MD, Srinivas Murali, MD, and Robert L. Hardesty, MD

Systemic Recombinant Tissue Plasminogen Activator Lysis for Left Atrial Thrombus Formation After Single-Lung Retransplantation
Christof Schmid, MD, D. C. Gulba, MD, B. Heublein, MD, J. Kemnitz, MD, PhD, and A. Haverich, MD

How to Do It

Preoperative and Postoperative Hemopump Support for Patients Undergoing Orthotopic Heart Transplantation
J. Michael Duncan, MD, Robert T. Baldwin, MD, and O. H. Frazier, MD

Retrograde Cardioplegia: Current Methods
W. Randolph Chitwood, Jr, MD

Current Review

Cardiac Pheochromocytomas
Victor A. Jebara, MD, Miguel Sousa Uva, MD, Arnaud Farge, MD, Christophe Acar, MD, Michel Azizi, MD, Pierre François Plouin, MD, Pierre Corvol, MD, Juan-Carlos Chachques, MD, Patrice Dervanian, MD, Jean-Noël Fabiani, MD, Alain DeLoche, MD, and Alain Carpentier, MD, PhD

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Journal Article

8. Wilkins EW Jr, Grillo HC, Scannell JG, Moncure AC, Mathisen DJ. Role of staging in prognosis and management of thymoma. Ann Thorac Surg 1991;51:888–92.

(List *all* authors if 6 or fewer; otherwise list first 3 and add "et al.")

Chapter in Book

12. Katz PO. Achalasia. In: Castell DO, Richter JE, Dalton CB, eds. Esophageal motility testing. New York: Elsevier Science Publishing Company, 1987:107.

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18. Larone DH. Medically important fungi: a guide to identification. 2nd ed. New York: Elsevier Science Publishing Company, 1987.

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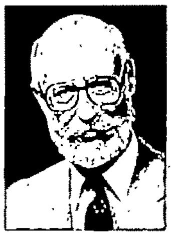

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Metaanalysis in Wound Healing

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Medical researchers use tensile strength testing as one of the methods to determine wound healing characteristics of an incision [1]. All surgical disciplines accept this technique and report it regularly in the journals [2–4]. The usual test method involves cutting strips containing the anastomosis and then pulling it apart. The force applied is known as the stress on the anastomosis. When the suture line breaks, the recorded stress is reported as the ultimate strength or tensile strength of the anastomosis.

See also page 80.

In the past few years, attempts have been made to simplify experimental design and achieve comparable data. One of these techniques is to measure the bursting pressure obtained by injecting an incompressible liquid (such as colored saline solution) into a closed tube that contains the anastomosis being evaluated. These data are reported as wound strength. Such an evaluation may be described as metaanalysis. Webster's lists among the definitions of "meta" a transformation often added to a name of a discipline designed to deal critically with the original one [5]. Auteri and associates [6] used metaanalysis to evaluate bronchial anastomosis in canine lung transplants. However, such transformed information is confusing and misleading. To understand the forces at work in a particular strength application, one must understand the basic concepts of experimental stress analysis [7].

A blood vessel, trachea or bronchus, or a segment of bowel can be represented as a thin-walled cylinder (Fig 1). Stress analysis theory can represent this tube using polar coordinates to define any force (P) applied to this segment in three primary directions. These forces act along the long axis (Z) direction (stretching the length of the cylinder); the angular (α) direction (stretching the circle wider); and the radial (R) direction (compressing the thickness of the wall). In addition to the three primary directions through which a force acts, there is an interrelation of any two coordinates known as the shearing force (τ). All five of these forces are mathematically represented by the Airy stress function, which comprises five simultaneous equations. Such a solution, although ideal, is impractical for a biologic system unless complex measurements can be taken. Most researchers therefore assume that the changes in the radial direction—the ones that alter wall thickness—are negligible. This decreases the Airy stress

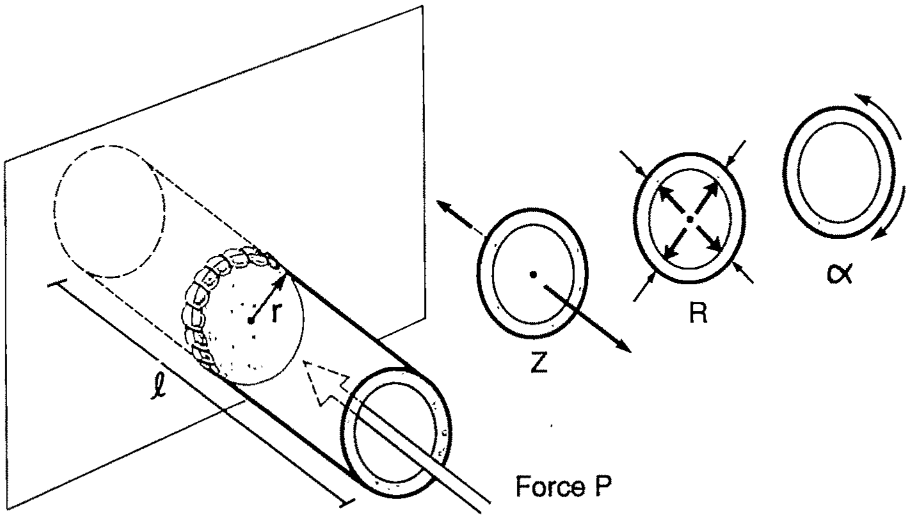

Fig 1. Schematic representation of a thin-walled cylinder with an anastomosis being stressed by an internal force (P). The cylinder has length (l) and radius (r). The primary stresses are represented by the longitudinal stress Z, the angular stress α, and the compressive stress R.

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function to two directions and only three simultaneous equations. Additionally, most investigators limit their evaluation to one dimension, the one at right angles to the anastomosis in question, because this force exerts all of its effect to pull apart the anastomosis. Thus, the stress (σ) in that direction can truly define the ultimate tensile strength.

When bursting strength is used to analyze an end-to-end anastomosis, investigators report only one number (P). However, this represents two-dimensional stress: the stress in the Z direction acting along the entire length of the segment and the stress in the α or angular direction acting along the circle. Moreover, the interrelationship between these two primary directions produces a shearing force (τ). This yields three simultaneous equations with only one overall force P known and no information available to break it into the two component stresses or vectors and their interrelationship (τ). Thus, it is not possible to accurately determine the force in the Z direction that primarily pulled apart the anastomosis. The answer obtained is far removed from the actual tensile strength or ultimate stress value desired. This also holds true for a longitudinal anastomosis. It would be impossible to separate out the angular stress from the longitudinal stress or the interactive shear force.

The use of bursting pressure, even for comparison, is problematic. Wound healing is a three dimensional process including the minor direction (angular for end-to-end anastomosis, and Z for longitudinal anastomoses). These changes are not characterized or evaluated in bursting pressure techniques. Yet, despite these major shortcomings, such metaanalysis will continue to appear in the journals. The reader is cautioned to interpret these data strictly as relative. They reflect only the overall strength of the entire object being tested and not the incision.

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Harvesting of the Internal Mammary Artery and the Healing Median Sternotomy

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Harvesting the internal mammary artery (IMA) certainly should have an effect on sternal blood supply and, therefore, healing of the median sternotomy. In this issue Carrier and his associates [1] present the results of a prospective clinical study designed to elucidate sternal blood flow as reflected by technetium-99m–methylene diphosphate tomography after median sternotomy for cardiac surgical procedures. Sixty-seven patients were studied in four groups. Group 1 (control) consisted of 9 patients undergoing myocardial revascularization with saphenous vein grafts alone and 3 patients undergoing valve replacements. Seventeen nondiabetic patients undergoing myocardial revascularization with a left IMA and saphenous vein grafts were studied in group 2. Eighteen nondiabetic patients undergoing myocardial revascularization with two IMAs and saphenous vein grafts made up group 3. The fourth and final group consisted of 20 diabetic patients undergoing myocardial revascularization: 5 with vein grafts alone, 8 with one IMA plus vein grafts, and 7 with two IMAs plus vein grafts. All patients were evaluated with ^{99m}Tc methylene diphosphate tomography 7 days after operation. Seven patients (5 from group 3 and 2 from group 4) had repeat scans 1 month after median sternotomy. The results suggest that median sternotomy alone causes no discernable decrease in sternal blood flow as measured by ^{99m}Tc tomographic scanning at 1 week after operation, but single IMA harvesting causes a significant decrease. This decrease is significantly greater when both IMAs are harvested. A bilateral decrease in flow is more common after double IMA harvesting, with consistent findings of decreased blood flow in the distal sternum.

See also page 115.

The clinical data presented are in agreement with investigational laboratory animal data published by us previously and allow a better understanding of blood flow to the sternum and, hence, healing after median sternotomy and IMA harvesting. Our first investigation of the effects of median sternotomy and IMA harvesting used sequential radioactive microsphere injections to delineate changes in sternal blood flow [2]. Median sternotomy alone had no significant immediate effect on sternal blood flow in rhesus monkeys. Harvesting of the IMA caused a significant (98%) decrease in radioactive counts in the ipsilateral hemisternum. This finding was uniformly consistent whether one or both IMAs were dissected. Moreover, we attempted to dissect the IMAs with virtually no use of the electrocautery so that possible collaterals would not be adversely affected. In a subsequent study using the same techniques in rhesus monkeys, we showed that the blood supply, as reflected by radioactive microsphere injection, had returned to control levels when sternal segments were studied 3 weeks after median sternotomy and IMA harvesting [3]. Synthesis of the three studies suggests that IMA harvesting causes a marked immediate decrease in sternal blood flow, followed by an increasing blood supply which allows early healing at 1 week, with return of blood flow at 3 weeks equal to presurgical levels. The fine details of the return of sternal blood flow after median sternotomy and IMA harvesting (such as the exact time when sternal circulation reaches presurgical levels) will be elucidated by subsequent laboratory and clinical investigations. For now we can accept that the majority of sternal blood flow has returned by 1 week and has achieved presurgical levels by the third postoperative week.

As the ipsilateral IMA is the primary blood supply to the hemisternum created by the median sternotomy, what sources provide the necessary collateral blood supply to revascularize the sternum? Arnold's [4] anatomic and our subsequent studies show that there is little immediate native collateral supply. In all probability there are three possible sources, which vary with the anatomic level of the sternum. The manubrium is least likely to be totally devascularized and has the largest number of collaterals. In harvesting the IMA, most often a few perforating arteries entering the upper part of the manubrium are not divided. These, when supplemented by blood from some few collaterals from intercostal arteries, the arteries from the strap muscles inserting on the manubrium, and the potential collaterals from the other half of the manubrium, provide an adequate secondary supply, which should make the manubrium the most difficult portion of the sternum to devascularize. The body of the sternum and the xyphoid are not quite as fortunate. The body has potential collaterals only from the intercostal arteries and perforating channels from the medial aspect of the pectoralis major muscle. The perforating vessels plus a portion of the sternal periosteum usually receive substantial cauterization currents when the IMA is harvested and before closure when the IMA bed is checked for hemostasis. The xyphoid is a little more

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fortunate in that it receives less coagulation current and has the ipsilateral rectus abdominis muscle for a potential source of collaterals. With cerclage closure wires generally encircling the sternal body in at least four places, periosteal and intercostal collateralization may be further impeded. The results presented by Carrier and associates [1] confirm that the distal portion of the sternum is more likely to suffer devascularization with harvesting of one or two IMAs. The extent of devascularization of the distal sternum probably has profound effects on sternal union, subsequent infection, and dehiscence.

The ultimate fate of a given sternotomy is not governed by blood supply alone. Many other factors obviously contribute to successful union. Closure method affects sternal healing, as was demonstrated by our group in a study conducted on baboons [5]. Although cerclage wires achieved similar sternal stability at 8 weeks after operation when compared with closure conducted by plates and lag screws, the new bone formation between the two sternal halves was less dense at 4 weeks. With less dense bone formation the potential collateral blood supply from the other sternal half has to be diminished. Carrier and associates [1] comment that closure methodology also may affect the final outcome in the healing sternotomy.

Surprisingly, Carrier and associates [1] present data that suggest that sternal blood flow in diabetics is the same as that in nondiabetics after comparable procedures. The numbers are large enough to support this conclusion at 1 week but are too small to draw any reasonable inferences at 1 month after operation. Hopefully these concepts can be confirmed by larger studies that give greater numbers of patients at more postoperative time intervals. If these data are confirmed by subsequent studies, further factors that affect sternal healing and control of infection in diabetics will have to be implicated to explain the increased incidence of median sternotomy complications in these difficult patients.

In summary, Carrier and his associates [1] are to be congratulated on providing us with some interesting data that give further dimensions to our knowledge of IMA harvesting and its effects on sternal blood supply. Their data provide interesting parts to our evolving completion of a jigsaw puzzle that has many parts. The questions raised by their study, particularly with respect to diabetic patients, encourage all to pursue laboratory and clinical investigations on this most interesting and important topic.

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Thoracic Surgery Participation in Cooperative Group Studies of Cancer Therapy

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All of us in thoracic surgery lost a friend when the National Cancer Institute ended funding for the Lung Cancer Study Group (LCSG). For 12 years this thoracic surgically directed group was the mainstay of thoracic surgical cooperative studies. During its life the LCSG activated 18 protocols and completed 17. It set standards for surgical staging of lung cancer [1], determined survival by TNM classification [2], and compiled modern morbidity and mortality statistics for lung resection [3]. Important questions about the role of radiation therapy in selected postoperative situations [4], the efficacy of limited lung resection [5], and tolerance and benefit of postoperative chemotherapy were answered [6].

With the demise of the LCSG, the nonsurgical cooperative cancer groups established Thoracic Surgical Committees to develop protocols. There are now Thoracic Surgical Committees or subcommittees in the Eastern Cooperative Oncology Group, the Radiation Therapy Oncology Group, the Southwestern Oncology Group, and the Cancer and Leukemia Group B. It is fair to say, however, that protocols involving thoracic surgery have never before been a high priority for these groups. The Eastern Cooperative Oncology Group's thoracic-related committees (lung, gastrointestinal, sarcoma) developed 97 protocols over the same 12-year period, of which only three involved thoracic surgery. One was closed after 12 months, accruing only 11 patients. The second, done with the Radiation Therapy Oncology Group, was basically a chemotherapy/radiation protocol for squamous cell carcinoma of the esophagus. It had a surgical resection option tacked on, but predictably it never produced meaningful surgical data. The third protocol studied the role of surgical resection in small cell carcinoma and was done in collaboration with the LCSG. The results of this study point out the importance of a committed thoracic surgical study group, for 75% of all patients came from the LCSG; 80% of the patients randomized to operation from the LCSG had complete resection, but only 55% randomized to operation from other sources had complete resection. The Radiation Therapy Oncology Group has had a similar track record, developing 27 protocols in the same 12 years, but no surgical treatment arms in any of its lung cancer protocols and only the one esophageal protocol with a surgical option mentioned above. Neither the Southwestern Oncology Group nor the Cancer and Leukemia Group B completed a large randomized cooperative thoracic surgical protocol.

The National Cancer Institute has created a considerable challenge for thoracic surgeons. We are now being asked to develop and perform thoracic surgical protocols in four different groups, each traditionally weighted toward either chemotherapy or radiation therapy. Most data managers in these groups are not familiar with thoracic surgical procedures and the many nuances that can make an operation a success or a failure. Detailed thoracic surgical quality assurance protocols must be developed. Substantial long-standing nonsurgical hierarchies exist within each group which may encumber the development of protocols targeted primarily for surgical patients.

Total funding for the four groups will be in excess of $20 million dollars in 1991 (as compared with about $1.2 million dollars annually for the LCSG). At each institution, these funds are now given to the radiation oncologist or medical oncologist who is the group's principal investigator and not to the thoracic surgeon who may be the actual principal investigator. It is reasonable to expect the National Cancer Institute to require a major commitment by these groups toward thoracic surgical protocols and to the thoracic surgeons who will participate in them.

We, as thoracic surgeons, realize that improved results in the treatment of thoracic malignancies will require a cooperative effort involving adjuvant and neoadjuvant therapy. It is, therefore, incumbent upon us to continue the important work of the LCSG. Continued diligence by members of the thoracic surgical committees, intergroup cooperation among the surgeons in the four groups, and active participation in the protocols by as many thoracic surgeons as possible will be essential. On the other hand, the Eastern Cooperative Oncology Group, the Radiation Therapy Oncology Group, the Southwestern Oncology Group, and the Cancer and Leukemia Group B must establish a level of responsiveness to thoracic surgery that has been lacking in the past. This goal will not be easily attained, but success will strengthen us as a specialty and our patients will be the ultimate beneficiaries. The LCSG has provided a standard of excellence by which to measure our accomplishments.

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Long-Term Experience With Descending Aortic Dissection: The Complication-Specific Approach

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We analyzed long-term results in 71 patients (45 men and 26 women) treated over 17 years for documented descending aortic dissection. Forty-nine patients were treated medically and 22, surgically. Actuarial survival was 65% at 1 year, 57% at 3 years, 50% at 5 years, and 28% at 10 years for the whole group. For the group treated medically, survival was 73%, 63%, 58%, and 25% at 1 year, 3 years, 5 years, and 10 years, respectively, and for the group treated surgically, 47%, 40%, and 28% at 1 year, 3 years, and 5 years, respectively. Ten (20.4%) of the 49 medically treated patients died early (5 of rupture), and 14 (28.6%) died late (8 of dissection). Five medically treated patients crossed over to surgical management for complications of dissection. Among the surgically treated patients, 6 underwent standard graft replacement of the proximal descending aorta, 8 underwent the fenestration procedure (with a standardized retroperitoneal abdominal approach), and 4 underwent the thromboexclusion operation. Specific analysis of fenestration in 14 patients (including some with persistent descending aortic dissection after replacement of the ascending aorta for dissection) found it to be safe and effective. Actuarial survival after fenestration was 77%, 77%, and 53% at 1 year, 3 years, and 5 years, respectively. Thromboexclusion was found effective, and postoperative studies confirmed thrombosis of the descending aorta with preservation of the lowest intercostal arteries. Fifteen of the 21 surviving medically treated patients agreed to return for follow-up imaging. Nine had thrombosis of the false lumen. An interesting radiographic finding was that 4 of the 15 restudied patients had a saccular aneurysm in the aorta at the level of the left subclavian artery. We recommend a complication-specific approach to the management of descending aortic dissection. Uncomplicated dissection is treated medically, whereas complicated dissection is treated surgically, with realized rupture treated by standard graft replacement, limb ischemia treated by fenestration, and enlargement or impending rupture treated by thromboexclusion.

(Ann Thorac Surg 1992;53:11–21)

Although often analyzed together, ascending and descending aortic dissections are different clinical entities with different therapeutic implications. For this reason, we chose to study descending aortic dissection specifically. Although survival to discharge from the hospital is an important end point for analysis, assessment of long-term survival is crucial to evaluation of therapeutic modalities. Accordingly, we review in this report our long-term experience at one institution with the treatment of descending aortic dissection.

Our intent is to determine the causes of early death, to determine the late outcome with medical or surgical treatment, to determine the long-term changes in radiographic appearance, and to evaluate a number of operations intended specifically for descending aortic dissection. These operations include standard graft replacement of the descending aorta, the fenestration operation, and the thromboexclusion operation. The data are used to make general therapeutic recommendations for short-term and long-term management. Because the operative mortality and paraplegia rates for conventional graft replacement remain extremely high even in the most recent large series (see Comment section), particular attention is paid to the possible merit of the nonconventional operations of fenestration and thromboexclusion.

Material and Methods

The case records of all patients treated for descending aortic dissection at Yale-New Haven Hospital between 1973 and 1990 were analyzed. For the purposes of this study, descending aortic dissection was defined as dissection involving the descending aorta (beyond the left subclavian artery) but not involving the ascending aorta or the aortic arch. The review identified 71 patients, the vast majority treated in the past decade. There were 26 women and 45 men. Age ranged from 25 to 88 years (mean age, 66.5 years). Only patients with a proven diagnosis of descending aortic dissection—on the basis of angiography, computed tomography, magnetic resonance imaging (MRI), operation, or autopsy—were included. Diagnosis was by angiography in 53 patients, by

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computed tomography in 38, by MRI in 5, and by operation or autopsy in 5. (Some patients had multiple studies.)

Follow-up ranged from 1 month to 17 years (mean follow-up, 3.3 years). Two medically treated patients and 1 surgically treated patient were lost to follow-up at varying intervals. With those exceptions, follow-up is complete on all patients up to the time of data analysis. All long-term survivors of medical treatment were invited to return for follow-up scanning by computed tomography or MRI to assess the anatomical behavior over time of the dissection. Initial and follow-up scans were available for 15 of the 21 long-term survivors of medical treatment.

Patients were managed medically unless specific complications developed. For purposes of analysis, patients were considered to be in the medical group if medical treatment was used up to the time of the first hospital discharge. Patients undergoing operation before the first hospital discharge were considered to be in the surgical group.

Three types of surgical procedures were carried out. Graft replacement of the proximal descending aorta was performed according to standard techniques using Dacron tube grafts and a variety of adjuncts for distal perfusion and spinal cord protection (including the "clamp and sew" technique, the use of heparin-bonded shunts, and the use of standard femoral-femoral bypass).

The fenestration procedures were performed according to a standardized technique, which we [1] have reported (Fig 1). The operation is performed at the abdominal level. With the left flank elevated, we approach the aorta retroperitoneally. The infrarenal aorta is transected. A generous window of the intimal layer is excised from the upper aortic segment up to the proximal clamp. The intimal and adventitial layers of the lower aortic segment are reapproximated with a continuous over-and-over suture (4-0 polypropylene). At this point, the upper aortic segment is reapproximated to the reconstituted lower aorta with a continuous suture (4-0 polypropylene). Thus, adventitia above is sewn to full-thickness aorta below.

The thromboexclusion operations are performed predominantly as described in 1981 by Carpentier and associates [2]. The procedure is performed through a midline thoracoabdominal incision from the suprasternal notch to the pubis. Cardiopulmonary bypass is not required. A large-caliber Dacron graft (22 to 26 mm) is attached end-to-side to the ascending aorta under side-biting control (Fig 2). The graft is routed through the pericardium into the right hemithorax and from there through the diaphragm, in front of or behind the left lobe of the liver, behind the transverse mesocolon, and into the retroperitoneum. The distal anastomosis is performed end-to-side to the infrarenal aorta under side-biting control or temporary infrarenal clamping. No Teflon reinforcing strips are required unless the distal abdominal aorta happens to be dissected. At this point, with permanent bypass of the thoracic aorta accomplished, the descending aorta is permanently occluded just beyond the left subclavian artery. For this purpose we have used a standard stapling device (TA 55, 4.8 mm; United States Surgical Corp, Norwalk, CT), as the permanent occluding clamp developed by Carpentier is not available in the United States. We have applied the stapler without reinforcing strips outside the aortic tissue.

Follow-up was obtained by review of hospital charts and office records, in-person office visits, telephone interviews with the patients or their families, and review of death certificates.

Actuarial survival is calculated by the Kaplan-Meier method and standard error, by the method of Peto. Age- and sex-adjusted expected survival figures are computed from US government statistics for 1988 [3].

Results

Actuarial survival for all patients is presented in Figure 3. Survival is 65% at 1 year, 57% at 3 years, 50% at 5 years, and 28% at 10 years. The upper curve represents the expected survival for an age- and sex-matched segment of the general population [3].

Medical Group

Among the patients managed medically, 10 (20.4%) of 49 died early (that is, during the initial hospitalization or within a few days of discharge). There was a preponderance of women in this group (6/10). The patients were elderly, with all but 1 more than 70 years of age. Four patients were judged not appropriate for aggressive care because of age or debility, and a fifth made this decision himself and signed out against medical advice. In a sixth patient, the diagnosis of dissection was made only after death. The remaining 4 patients died despite aggressive medical treatment. There was a cluster of deaths in the first 4 days, with the remainder scattered over 2 weeks after presentation.

Five patients died of rupture of the aorta. (Rupture occurred on days 1, 3, 11, 12, and 16.) Two died of vascular complications of the dissection (mesenteric infarction in 1 and occlusion of the thoracic aorta in the other). Three patients, all with prior cardiac histories, died of primary cardiac dysfunction during medical treatment of dissection. Extravasation of blood into the periaortic tissues or body cavities had been noted in 2 of the 4 patients with known dissection who had rupture (the fifth patient who died of rupture had an undiagnosed dissection). Neither of the 2 patients with documented extravasation underwent operation, as both were judged not suitable from an overall standpoint for aggressive surgical treatment.

There were 14 late deaths (28.6%) among the 49 medically treated patients. The deaths occurred from 3 months to 11 years after diagnosis of descending aortic dissection, with a concentration in the first year. Eight (57.1%) of the late deaths were judged likely to be dissection related. Known or suspected rupture and unexplained sudden death were included in this category. One of these patients died during operation for expansion of the dissected aorta. Three of the late deaths were primarily cardiac related and not dissection related. Three late deaths were neither dissection related nor cardiac related (1 each due to antecedent chronic renal failure, malignancy, and pneumonia).

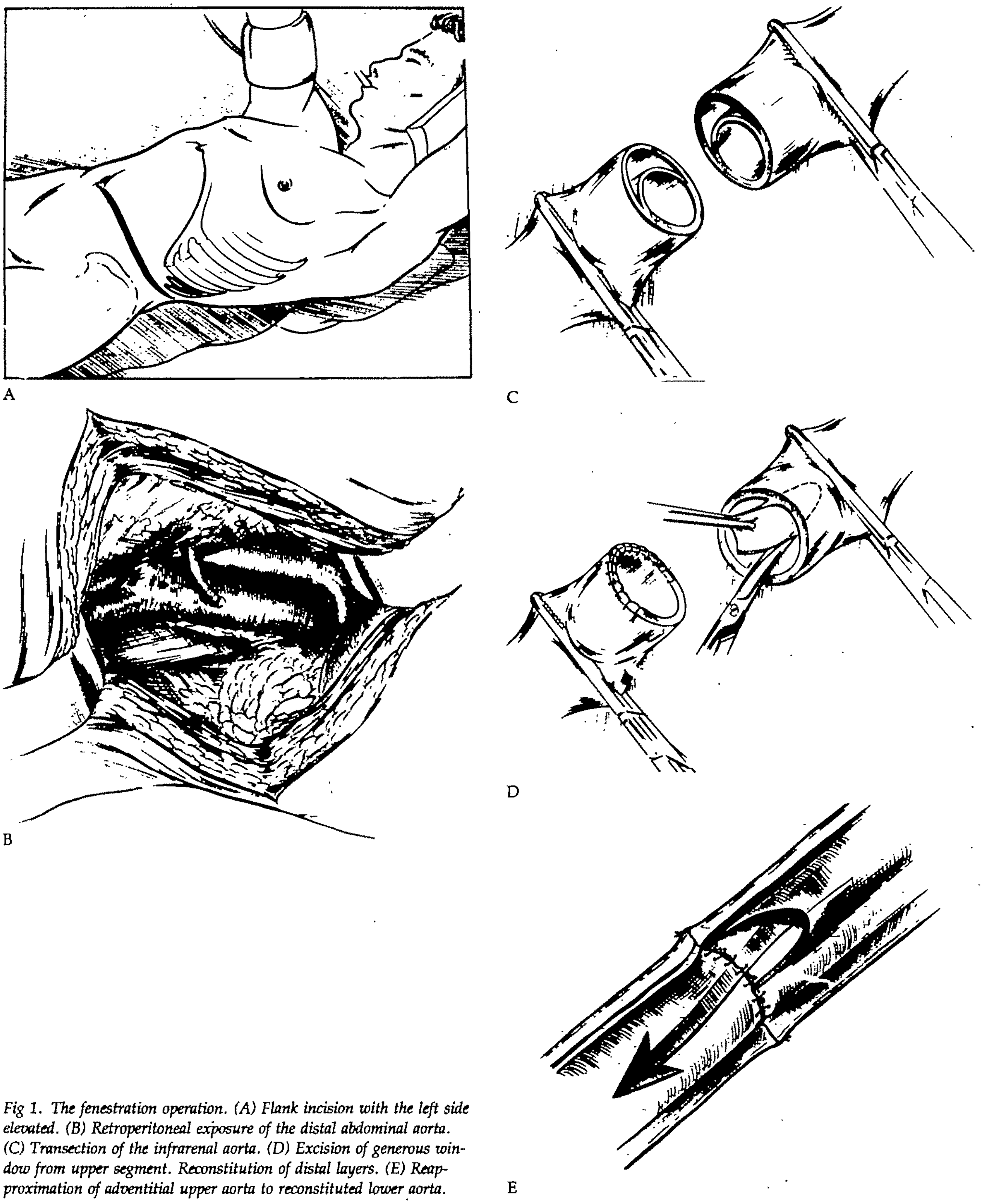

Fig 1. The fenestration operation. (A) Flank incision with the left side elevated. (B) Retroperitoneal exposure of the distal abdominal aorta. (C) Transection of the infrarenal aorta. (D) Excision of generous window from upper segment. Reconstitution of distal layers. (E) Reapproximation of adventitial upper aorta to reconstituted lower aorta.

Twenty-one (42.9%) of the 49 patients in the medical group remain alive after follow-up of 1 year to 17 years. Five patients crossed over to surgical treatment: 1 for hepatorenal bypass for hypertension, 1 for resection of a ruptured abdominal aortic aneurysm, 1 for axillobifemoral grafting for acute aortic occlusion, and 2 for replacement of the ascending aorta for acute dissection. Among the last 2 is found the longest survivor, who has lived 17 years after the diagnosis of descending aortic dissection.

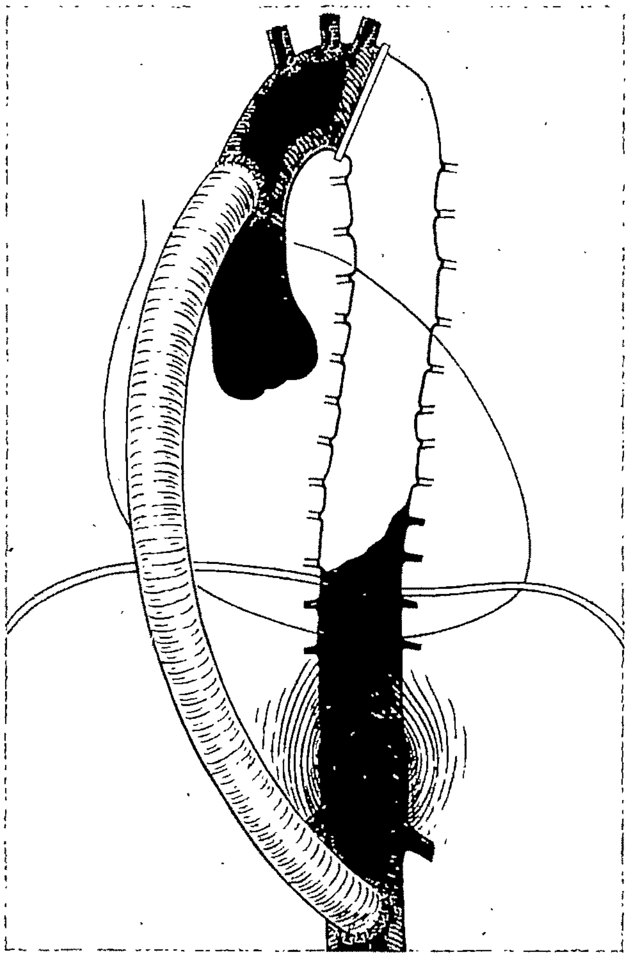

Fig 2. The thromboexclusion operation. See text for details.

Actuarial survival for the medical patients is presented in Figure 4. Survival is 73% at 1 year, 63% at 3 years, 58% at 5 years, and 25% at 10 years.

Fifteen of the 21 surviving patients in the medical group agreed to return for radiological follow-up at intervals ranging from 1 month to 17 years from the time of dissection. Follow-up was done by angiography, computed tomographic scan, or MRI scan. Magnetic resonance imaging scan has been preferred in recent years. Three-dimensional reconstruction by computer assimilation and graphic representation of MRI data has been used to aid analysis of follow-up data.

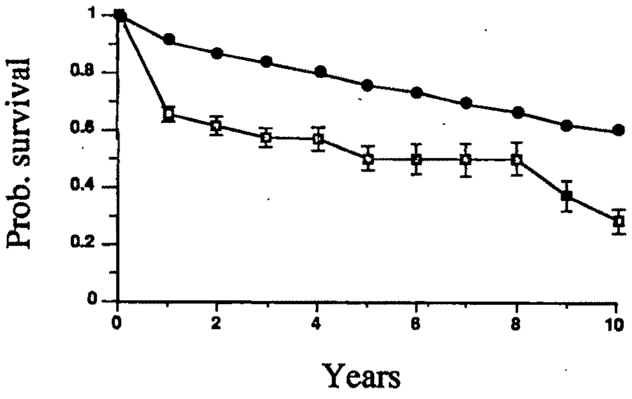

Fig 3. Actuarial survival for all patients (± standard error). Upper curve represents expected survival for age- and sex-matched segment of the general population.

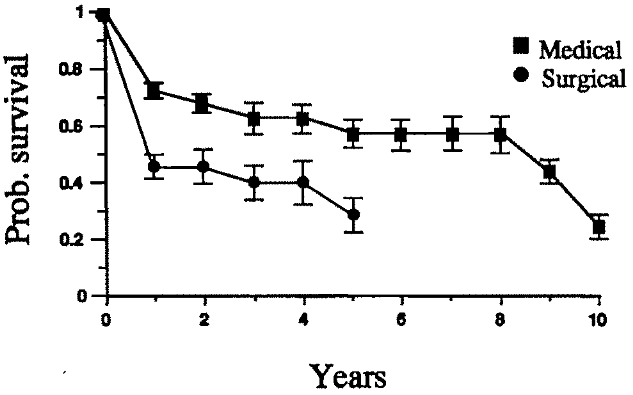

Fig 4. Actuarial survival (± standard error) for medical and surgical groups.

Three factors were assessed on repeat radiographic analysis: (1) the fate of the false lumen (patency or thrombosis), (2) the change in overall transverse diameter of the aorta, and (3) the change in linear extent along the aorta. The false lumen remained patent in 6 patients and thrombosed during follow-up in 9. Seven showed transverse enlargement: 2 showed increase in transverse diameter throughout the dissection, 1 had enlargement of a contiguous abdominal aortic aneurysm, and 4 had development of a localized aneurysm in the aorta at the level of the left subclavian artery. It was striking that these four aneurysms, located just at the terminus of the aortic arch, had been missed on computed tomograms (because of the axial nature of the images) but were easily seen on MRI (in sagittal images) (Fig 5). The relative frequency with which these proximal arch aneurysms were seen argues for the importance of MRI scanning as a follow-up tool. Three patients showed changes in the linear extent of the dissection along the aorta: 1 had dissection distally over time, and 2 showed proximal extension into the ascending aorta. These 2 patients survived replacement of the ascending aorta; one procedure was carried out urgently and one, electively.

Surgical Group

Twenty-two patients underwent surgical treatment. Six had standard graft replacement of the proximal descending aorta with a variety of approaches to perfusion and cord protection, 8 underwent the fenestration procedure, and 4 underwent the thromboexclusion operation. Four had miscellaneous procedures (aborted graft replacement after cardiac arrest in 1, simple suture of the bleeding site in 1 patient taken to the operating room in cardiac arrest, and specific limb and visceral revascularization procedures in 2). Of the 6 patients who underwent standard grafting of the proximal descending aorta, 4 died and 2 survived long term. Of the 4 who died, 3 patients had sustained cardiac arrest and undergone cardiopulmonary

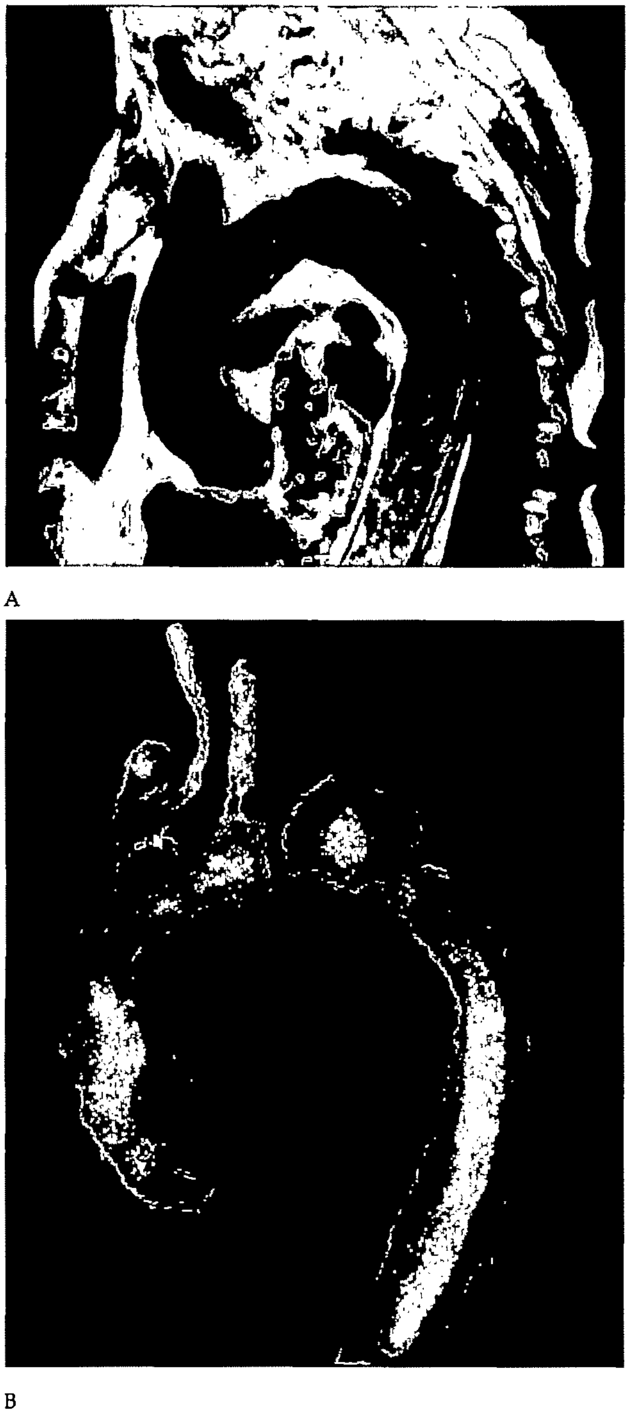

Fig 5. (A) Sagittal magnetic resonance image of perisubclavian aneurysm. (B) Three-dimensional computer-enhanced depiction of same aneurysm.

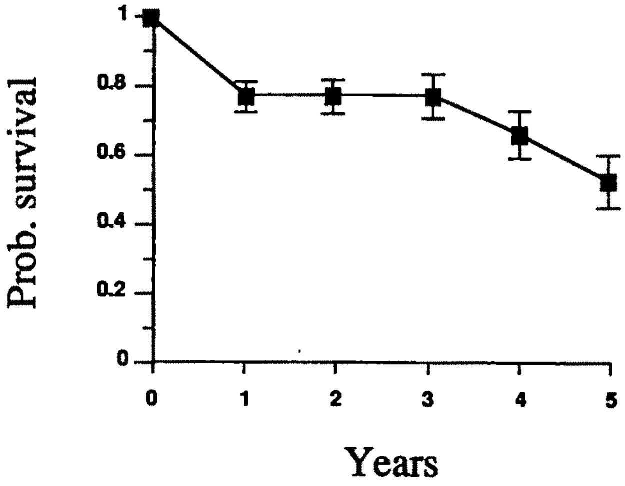

Fig 6. Actuarial survival (± standard error) for 14 patients undergoing fenestration.

resuscitation before the operative procedure. One of the 4 had been on a long-term regimen of steroids and died of insurmountable anastomotic difficulties. Overall actuarial survival for all patients in the surgical group is illustrated in Figure 4. Survival was 47% at 1 year, 40% at 3 years, and 28% at 5 years. Survival was adversely influenced by the high early mortality, which reflects the patients taken to the operating room with realized rupture. Correcting for this early mortality, the slope of the survival curve is roughly similar to that for the surviving medical patients and just somewhat worse than that for the general population.

For most of the study period, the fenestration operation was used as the procedure of choice for the complication of limb or organ ischemia resulting from descending aortic dissection. Fenestration was not used for other complications. We have performed this procedure in 14 patients, most from this group with descending aortic dissection, but also in some with the "equivalent" of persistent descending dissection after graft replacement of the ascending aorta for ascending dissection. Leg ischemia was the indication for intervention in 12 patients and renal ischemia (with uncontrolled hypertension), in 2. Two patients with leg ischemia also had paraplegia and spinal cord ischemia as an associated indication.

Successful reperfusion was achieved in 13 (93%) of the 14 patients. The pulse to the lower extremity was restored in all patients. The only leg that was lost had been ischemic for a prolonged period before fenestration and was amputated despite restoration of the femoral pulse by the fenestration procedure. Both cases of renal ischemia resolved with fenestration. One of the 2 cases of paraplegia improved with fenestration.

Long-term actuarial survival after fenestration is indicated in Figure 6. Mean follow-up is 5 years. Two patients have been followed up for 9 years and 1 for 12 years. Actuarial survival is 77% at 1 year, 77% at 3 years, and 53% at 5 years. Only 3 of the 11 survivors have died during follow-up, 1 at 4 years, 1 at 5 years, and 1 at 9 years. One patient died of myocardial infarction. Cause of death is unknown for the other 2 patients. To our knowledge, no aortic or ischemic problems have occurred in the survivors. There does not appear by chest roentgenography to be any pattern of enlargement of the fenestrated aortas over time, a finding suggesting a possible protective effect of fenestration.

We have used the thromboexclusion operation for expansion or impending rupture of the dissected aorta. This experience encompasses 4 patients, all operated on within days or weeks of the acute presentation. One patient died intraoperatively of hemorrhage and 3 survived. One died at 6 months of malignancy. Two are alive at 3 and 3½ years. We have found on routine follow-up angiography that the descending aorta does indeed thrombose within days of the procedure (Fig 7). The postoperative angiograms also show that the low intercostal arteries do remain patent. There has been no rupture, extension, or other late complication of the dissection in the survivors of this operation.

Comment

As shown in Figure 3, after the early deaths have occurred, the slope of the survival curve for all patients approximates that of the general population. Our long-term follow-up of the natural history of descending aortic dissection is in keeping with prior reports. The Massachusetts General [4], the Stanford-Duke [5], and the Texas [6] series are among the best-known studies of aortic dissection. The long-term survival rates for descending aortic dissections in those studies are roughly similar to those of the present study. Direct comparison of rates is difficult because of the many variables inherent in specific tabulations (for example, medical or surgical treatment, acute or chronic dissections, and inclusion or exclusion of hospital deaths). In a preliminary abstract, Masuda and colleagues [7] reported survival rates for medical treatment of descending dissection that are considerably higher than those in other series (92% at 1 year, 89% at 5 years, and 76% at 10 years). In particular, the very low rate of early deaths stands out.

We do not see any purpose to statistical comparison of medical and surgical survival in our series, as these treatments were applied to different groups of patients. Specifically, surgical management was confined to patients with major complications of dissection. Both the medical and surgical survival curves reflect the high early mortality, which was even greater in the surgical group, where it was influenced by the numerous patients taken to the operating room with realized rupture and in cardiopulmonary arrest. For patients discharged after medical or surgical treatment, the slope of the survival curve for medical and surgical treatment approximates that depicted for an age- and sex-matched general population (which has a 4.4% per year attrition).

Other series have not concentrated specifically on fenestration or thromboexclusion as specific primary surgical treatments for descending aortic dissection. We believe these procedures merit attention.

Fenestration

Fenestration was originally performed by Gurin in 1935 and was the first surgical treatment of any kind for aortic dissection. Although fenestration is mentioned sporadically in the surgical literature, the procedure has received little specific scientific attention as a primary surgical treatment for descending aortic dissection. Fenestration was conceived because it mimicked the decompression of the false lumen seen in spontaneous survivors of aortic dissection. Fenestration makes intuitive sense (Fig 8). It is easy to understand how complete decompression of the false lumen may restore flow to compromised branches.

We [1] recently "revisited" this procedure and analyzed its effectiveness. The present report expands and extends the experience in our earlier report. In general, fenestration can be accomplished with minimal insult in these critically ill patients, as it is performed with minimal blood loss through the retroperitoneal approach. Despite the tenuous appearance of the upper adventitial aorta, we have found it to hold sutures and restrain the bloodstream in all instances. Although there are other reports of fenestration in the literature (summarized in [1]), most were case reports or reviews of large series of aortic dissections in which a handful of patients underwent fenestration. We are not aware of other reports that have specifically examined the safety and utility of fenestration as a primary surgical modality in a series of patients.

It is important to note that fenestration relieved not only limb ischemia but also renal ischemia in the few patients with this additional complication. Correction of leg ischemia connotes that fenestration restored perfusion below the infrarenal level of the procedure. Correction of the renal ischemia connotes that fenestration restored perfusion above the anatomical level of the procedure as well.

It is instructive to compare fenestration with the more widely used procedure of graft replacement of the proximal descending aorta. Fenestration avoids thoracotomy; avoids the issue of paraplegia as a complication of surgical intervention; avoids the issues of circulatory adjuncts for cord protection, cardiac unloading, and distal perfusion; and avoids prosthetic materials entirely. Furthermore, fenestration addresses the limb ischemia directly. It is not unusual to perform an appropriate graft replacement and have limb ischemia persist. In the Stanford series [8], 8% of patients had persistence of a peripheral vascular complication after replacement of a segment of thoracic aorta and required another peripheral vascular procedure directed specifically at that defect. Especially because all procedures for aortic dissection are palliative, fenestration becomes attractive because of its simplicity and utility.

Thromboexclusion

Although Carpentier and colleagues [2] originally described this procedure for both ascending and descending aortic dissections, we have found it appropriate for descending dissections only. As thromboexclusion cannot control an already ruptured dissection and as the fenestration operation manages the complication of limb ischemia, we have reserved thromboexclusion for the complication of enlargement or impending rupture. We have considered continued or renewed pain, especially in the face of a new bloody pleural effusion, to be indicative of impending rupture. The advantages of the thromboexclusion procedure are many: (1) the entire operation is

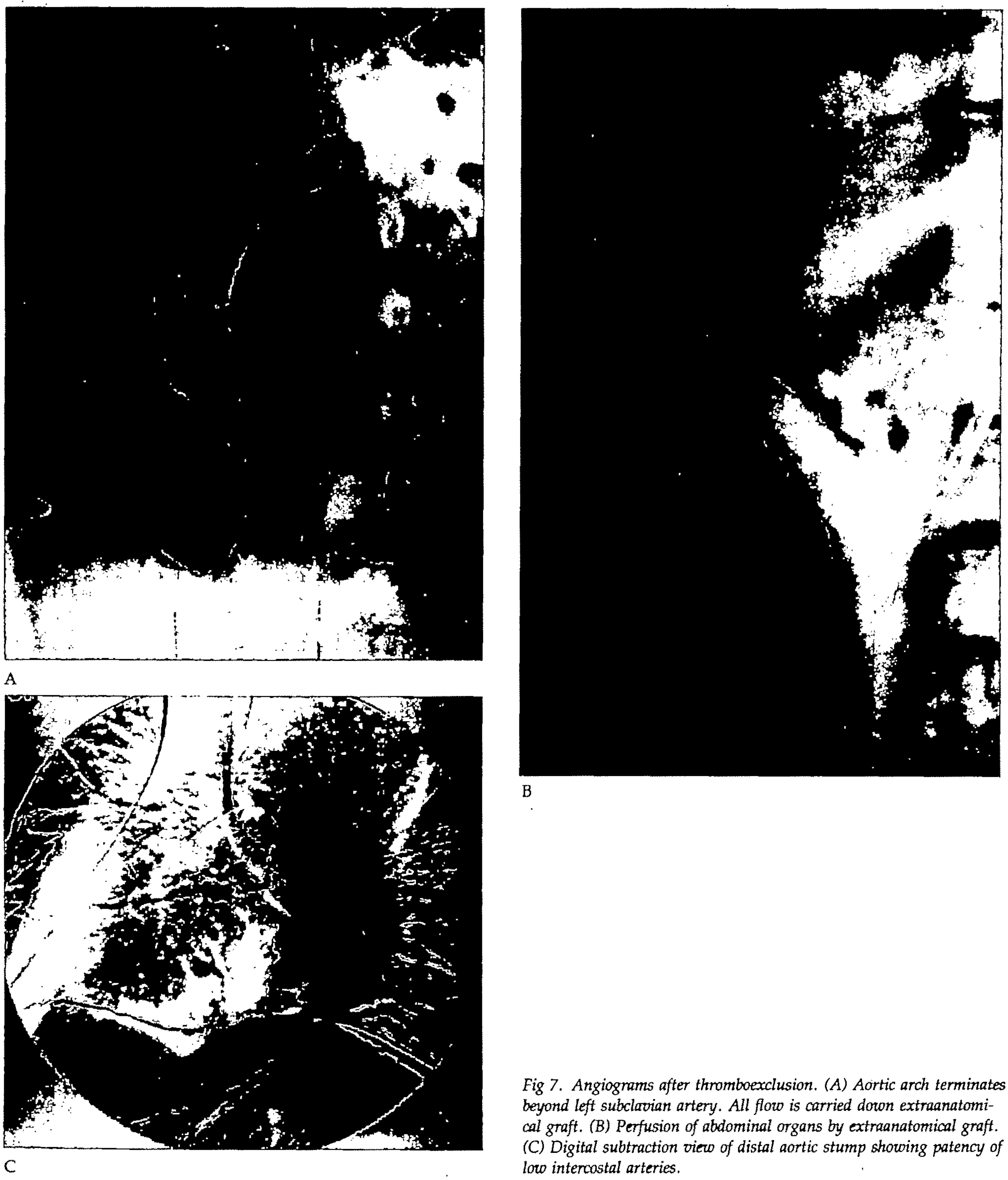

Fig 7. Angiograms after thromboexclusion. (A) Aortic arch terminates beyond left subclavian artery. All flow is carried down extraanatomical graft. (B) Perfusion of abdominal organs by extraanatomical graft. (C) Digital subtraction view of distal aortic stump showing patency of low intercostal arteries.

performed on nondissected aorta; (2) as there is no clamping of the descending aorta, questions of cardiac unloading, lower-body perfusion, and spinal cord protection do not arise; and (3) the entire descending aorta is excluded by thrombosis (as opposed to the replacement of only a small segment of proximal descending aorta in a conventional graft operation). The concept behind the thromboexclusion operation is that gradual thrombosis of the descending aorta will occur in the excluded blind segment. The hypothesis is that this gradual thrombosis will allow adaptation by the body with collateral formation to decrease the incidence of paraplegia. It is further

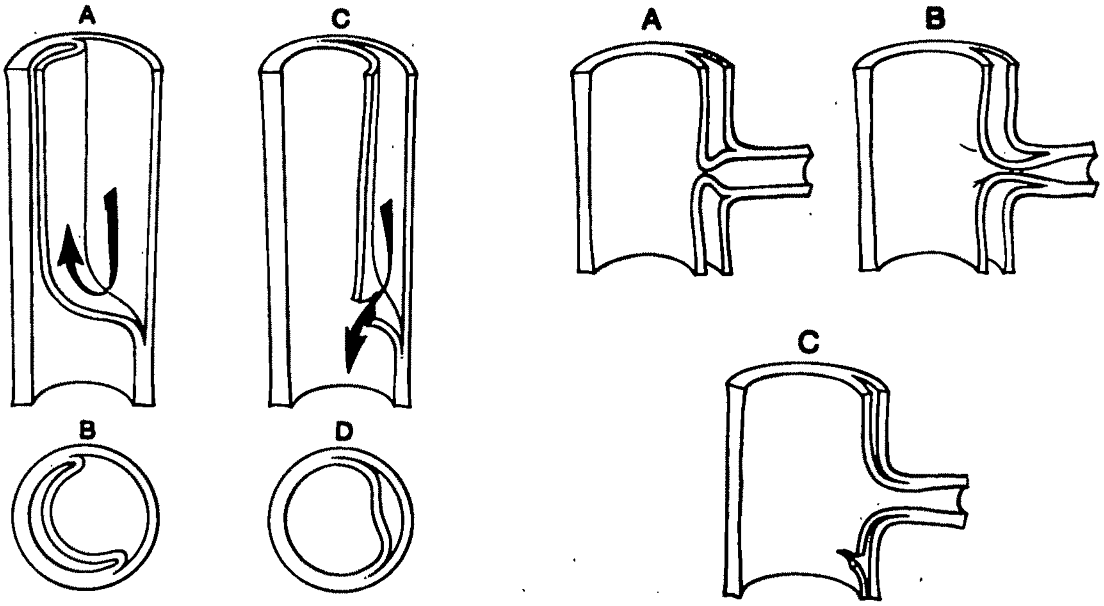

Fig 8. Intuitive representation of physiology of fenestration. (Left) Fenestration restores caliber of native aorta (by relieving distention of false lumen) (A and B, before fenestration; C and D, after fenestration). (Right) Fenestration restores patency of branch vessel (by relieving distention of false lumen) (A, early after dissection; B, with extension of dissection into breach; C, after fenestration).

hypothesized that low thoracic intercostal arteries carrying major flow, as would be expected for major spinal cord tributaries, will remain patent. Further, it is presumed that thrombosis of the descending aorta will prevent rupture or extension of the dissection.

Our limited experience supports these hypotheses. Our postoperative angiograms have confirmed that thrombosis of the descending aorta occurs within days. We have also confirmed that the low intercostal arteries remain open. (Both points are illustrated in Figure 7.) Our limited experience has indicated that the procedure does control the dissection process, preventing rupture and extension.

We hasten to point out some trouble areas in performance of the thromboexclusion operation. One is that no clamp or stapler appropriate for permanent occlusion of the aorta at this level is currently available in the United States. Although Ergin and associates [9] have been pleased with conventional stapling devices for use on the thoracic aorta, we have found that a large aorta can overwhelm the conventional staples. Odagiri and associates [10] in Japan have had experience similar to ours, which has led them to develop a stapler specific for the thoracic aorta. This stapler allows a closed height of 3 mm (as opposed to 2 mm for the conventional device), which can accommodate the thickness of the thoracic aorta and two buttressing Teflon strips. (This device is not yet ready for general clinical use [Odagiri S; personal communication, 1990].) We have begun performing the stapling under inflow occlusion to allow collapse of the aorta so that the conventional stapler can more easily control the aorta.

We also caution about surrounding the thoracic aorta in an acute dissection beyond the subclavian artery through the median sternotomy. It is very easy to enter the dissection plane, and we had severe bleeding related to this problem in 1 patient. Odagiri and co-workers [10] reported this same problem and suggested stapling the aorta proximal to the left subclavian artery to allow better exposure and a safer margin from the thin dissection plane. They have grafted the subclavian artery separately after such occlusion of the aortic arch. An extension of the sternotomy into the left neck may also be useful in improving exposure.

Despite the theoretical advantage of the operation regarding paraplegia, we did encounter one instance of paraplegia occurring 3 days after operation, presumably as thrombosis propagated along the aorta toward the diaphragm. As with the case of paraplegia that Carpentier [11] reported after thromboexclusion, we believe that in our patient, compromise of collateral flow to the spinal cord through the left subclavian artery may have contributed to the paraplegia. Although paraplegia has been seen rarely with thromboexclusion, this procedure still compares favorably with conventional replacement of the entire descending aorta, which is known to carry a high rate of paraplegia (21% to 40% in the series of Crawford and associates [12]).

The Complication-Specific Approach

We find our natural history data on the long-term follow-up of patients managed medically for uncomplicated descending aortic dissection to support the posture that this is essentially a medical condition. Even the Stanford group [8] is moderating its previous position favoring routine operative management. The recent report [5] combining the Duke and Stanford data further confirms that a routine surgical approach is not necessary. Because surgical intervention for descending dissection is palliative, we are swayed by the realization that a complication-directed approach seems reasonable.

Although the debate concerning whether or not to operate has been brisk, little attention has been given to the question of which operation to do. It was presumed that to operate meant to carry out the standard replacement of the proximal descending aorta (or the "most diseased" portion of the descending aorta—a difficult distinction at best). Our experience supports a selective operative approach with a choice of graft replacement, fenestration, or thromboexclusion depending on the patient's presentation and status.

On the basis of the experience reported here, we recommend the following approach to acute descending aortic dissection: We advocate not a dogmatic single-operation surgical approach, but rather one that is *specific for the complications* manifested by the dissection in a particular patient. If there are no complications—that is, no rupture or impending rupture, no extension or failure to control symptoms, and no organ ischemia—the dissection can be treated medically. Careful and regular follow-up is required to monitor for expansion, which can mandate late intervention.

If the dissection is complicated at the time of presentation, then prompt surgical intervention is indicated. We use a complication-specific approach. For rupture, we continue to practice graft replacement of the thoracic aorta. If the complication is expansion or extension, we favor the thromboexclusion procedure. If the complication is limb or organ ischemia, we favor the fenestration operation.

It should be pointed out that both fenestration and thromboexclusion are most useful in acute or subacute dissection. All of the procedures in our series were carried out within days or weeks of the original presentation. The patients were often critically ill at the time of the procedure, with life or limb in great jeopardy. In the chronic phase, months or years after initial dissection, the conventional resectional approaches used for nondissecting arteriosclerotic aneurysms of the descending aorta become applicable.

Although new approaches, such as the elective use of deep hypothermia recently reported by Kouchoukos and co-workers [13], promise to make descending aortic operations safer in the future, the beauty of the fenestration and thromboexclusion procedures is that they obviate entirely the problems of circulatory assistance and protection of the lower body and spinal cord.

Recent reports have described new and less invasive techniques for aortic dissection, including the Ivalon sponge occlusion technique [14], the temporary cylinder-type balloon [15], and the permanent balloon-expandable intravascular stent [16]. These reports involve primarily laboratory studies and some very preliminary clinical work. The techniques have not yet found their way into clinical practice at our institution or generally elsewhere. Although they hold promise for the future, these techniques are not yet included in our paradigm for the complication-specific approach to descending aortic dissection.

It is important to emphasize the relative simplicity and safety of the techniques of fenestration and thromboexclusion. Only 1 patient undergoing either of these procedures died during operation. Subsequent survival was realized almost uniformly unless the patient's preoperative overall status had already been severely compromised. This tolerance of the surgical procedure is in contradistinction to the 40% mortality for acute descending aortic dissections and the 64% mortality for acute descending aortic dissections with vascular complications seen with conventional grafting in the recent Stanford-Duke series [8].

The recommendations in this report are provisory. An inherent limitation in the present study is that it is a retrospective, nonrandomized review. Prospective analysis is difficult or impossible in such cases. We follow with interest the approaches used at other centers. We look forward to accumulating more experience and more long-term follow-up on our own patients to reassess our complication-specific approach, which is recommended only on a preliminary basis as data accumulate.

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DISCUSSION

DR LARS SVENSSON (Houston, TX): I congratulate Dr Elefteriades for this review and for raising some very important questions. First, when do we operate on patients with aortic dissection, and second, what operation should be performed?

My colleagues and I [1] in Houston recently reviewed our series of 690 patients who underwent operation for aortic dissection. Of these, 389 had either thoracoabdominal or descending aortic repair. The survival rate for patients recently operated on, irrespective of whether the dissection was acute or chronic or of the extent of the resection, was approximately 95%. We think that surgical intervention should be aggressively undertaken for patients with aortic dissection in whom medical treatment fails. Our indications for operation have been failure of medical treatment, persistence of pain after therapy, aneurysmal segment larger than 5 cm, and occurrence of complications.

You raised the issue of computed tomographic scanning and magnetic resonance imaging for patients. The question is, of course, What size should the aneurysm be to operate? In our series, we noted in 12% of patients with ruptured aneurysms, the aneurysms were smaller than 5 cm. There is supporting evidence for this observation from the Japanese literature and Dr Glower's study of the combined Stanford and Duke University experience. Dr Glower indicated at the American Heart Association meeting that there is some risk of rupture in aortas smaller than 5 cm, although the risk increases greatly in aortas larger than 5 cm. However, we do have to consider the risk of paraplegia and paresis after operation, which you raised, and balance this with the benefit of preventing late rupture.

Concerning the operative procedures, we have not used fenestration in our recent series because we do not think that it solves the problem or prevents rupture. Nor do we use thromboexclusion, as it has been reported that with thromboexclusion, paraplegia can still occur, rupture can occur, the mortality rate for surgical intervention is not reduced, and migration of the clamp occurs. We found in our study that the most important predictor of both late rupture and late death was residual aneurysmal disease. I would be interested to hear your views about your long-term follow-up of patients with residual aneurysmal disease because in these patients you have undertaken palliative treatment. Particularly, how often do you undertake computed tomographic and magnetic resonance scanning? We believe scanning should be done every 6 months if medical treatment is used.

DR ELEFTERIADES: The patients in our Yale series had predominantly acute dissections. We do not see a lot of chronic dissections. The motivation to seek other surgical alternatives was that in most series, the mortality and paraplegia rates remain high. The most recent report from the combined Stanford-Duke series has a 40% to 60% mortality for patients with acute descending dissections, the 60% being for patients with vascular complications like ours. In Dr Crawford's extensive reports, the paraplegia rates with resection of the entire segment with disease range from 20% to 40%.

As for long-term follow-up, the possibility of rupture has been a concern. We have not encountered rupture after fenestration. After thromboexclusion, we see clearly in our follow-up angiograms that nearly all of the descending aorta does thrombose. The possibility of rupture in the abdominal segment remains, and that is something that we will be following up closely.

As for the occurrence of paraplegia, that has been reported after thromboexclusion. We have seen 1 case at Yale, and we know that 1 case has occurred in France as well.

As for migration of the clamp, that is certainly an important concern. Because we do not have access to the French clamp in the United States, we have been using a regular stapler, and that is secure from migration. However, a regular stapler with the 4.8-mm staples can be overwhelmed by a large aorta. We are not totally comfortable with this portion of the thromboexclusion technique and think that a stapler specific for the thoracic aorta should be developed.

DR C. E. ANAGNOSTOPOULOS (Stony Brook, NY): I compliment the Yale group for an approach to acute aortic descending dissection that we have been discussing for some time, namely, the complication-specific approach. Regardless of what the surgical results are, and there have been many series with early mortality of 4% or 5%, the combined renal and neurological complications of operation on the descending aorta have not changed much over the last 35 years.

My question concerns specifically the clotted false lumens. We reported earlier with Dr Sanderson that there should be a reappraisal of the "safety" of the clotted false lumen, as promulgated by McFarlane. We had found 2 patients with rupture at the time of the report and noted 2 subsequently. We do not say that the presence of a clotted false lumen is an automatic indication for continuing medical therapy. Do you have a specific follow-up of your 9 patients with clotted false lumens?

DR ELEFTERIADES: We are very interested to continue the follow-up of those patients to see what does happen and how protective a clotted false lumen is. We share the concerns that it is not totally protective. One of the 4 patients with a saccular aneurysm just beyond the left subclavian artery has a clotted false lumen. Obviously it has not protected him from localized dilatation of the aorta.

DR FRANCIS ROBICSEK (Charlotte, NC): The procedure of thromboexclusion as described by French authors does not make much sense to me. To leave an aorta exposed to both blood pressure and pulsating flow, despite elimination of the shear factor and velocity, certainly cannot be called a safe procedure.

In several instances my associates and I have used a modification of this technique, namely, we have occluded the involved segment both proximally and distally. The operation usually was done in two stages. First, we did an ascending aorta–infrarenal aorta anastomosis. Then, a few days later, we entered the left chest through a limited thoracotomy and excluded the dissected or aneurysmal segment. In case of emergency, the same operation can be done in one stage. With this modification, the involved segment is completely excluded, and you do not have to worry whether or not nature does its work by spontaneous thrombosis. It converts an unsafe procedure into a completely safe one. We have observed patients in whom we used this technique for more than 5 years now, and we have never seen a late rupture or a further dilatation of a completely occluded segment.

DR ELEFTERIADES: The point concerning distal surgical occlusion of the aorta is an important one. Although angiography confirms spontaneous thrombosis after performance of the operation as originally described by the French, rupture remains a theoretical concern, especially as numbers of patients are small and follow-up limited.

It is important in evaluating thromboexclusion (or fenestration) to keep in mind that with the conventional replacement of a segment of the proximal descending aorta, there is a lot of aneurysmal disease left behind. Our intention here is to provide an option for relatively acute dissections. The amount of aorta that remains perfused after thromboexclusion is certainly going to be less than what customarily remains after conventional replacement of a small proximal portion of the descending aorta.

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Operative Risks and Long-Term Results of Operation for Left Ventricular Aneurysm

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A review of 336 consecutive patients who underwent repair of left ventricular aneurysm from 1978 to 1989 disclosed that partial resection of the aneurysm and conventional closure of the ventriculotomy was performed in 281 patients, inverted T closure in 17, and endocardial patch in 38. These two latter techniques were developed in an attempt to restore normal left ventricular geometry. The operative mortality was 6.8% (23 patients). A stepwise logistic regression analysis of various preoperative clinical, hemodynamic, and angiographic variables revealed that left ventricular ejection fraction of 0.20 or less, age greater than 60 years, previous myocardial revascularization, lack of angina, and New York Heart Association functional class IV were independent predictors of operative mortality. The technique of repair was not a predictor of outcome, but when patients with poor left ventricular function were analyzed separately, the operative mortality was reduced from 12.5% to 6.5% when newer techniques were employed. Patients were followed up during a mean of 6.3 years. There have been 51 late deaths, 45 cardiac. Cox regression analysis indicated that poor left ventricular function and left main coronary artery stenosis were the only two predictors of late mortality. The actuarial survival at 10 years was 63% ± 4%. Most patients (88%) are in New York Heart Association class I or II. These data indicate excellent long-term results after repair of left ventricular aneurysm. Newer techniques of repair are valuable in patients with poor left ventricular function.

(Ann Thorac Surg 1992;53:22–9)

Surgical repair of left ventricular aneurysm (LVA) was first performed by Charles Bailey in 1955 [1]. A large clamp was applied to the neck of the aneurysm and, after its base was sutured, a segment measuring 5 by 7 cm was resected [1]. The first resection under cardiopulmonary bypass was reported by Cooley and associates in 1958 [2]. The operative technique for resection of LVA remained unchanged for almost three decades. As surgeons recognized the importance of left ventricular geometry in left ventricular function, attention was turned to new methods of repairing the aneurysm to improve surgical results. In his Honored Guest's Address to the American Association for Thoracic Surgery in 1984, Adib Jatene from Brazil introduced the concept of left ventricular "reconstruction" for patients with chronic LVAs [3]. That was a timely presentation because many surgeons were looking at different methods to repair the left ventricle in such patients. It is now generally accepted that whatever technique one employs to repair an LVA, restoration of left ventricular geometry is important to optimize left ventricular function.

This report is a review of our experience with different methods of repairing LVAs, the operative risks associated with them, and the long-term results.

Material and Methods

Patients and Operative Technique

From January 1978 to December 1989, 365 patients underwent operation for LVA. A careful review of the operative notes and left ventricular angiographic reports indicated that 29 patients had had small apical LVAs that were repaired by simple plication with a few sutures. These patients were excluded from this study. The remaining 336 patients had resection of part of the aneurysm and repair of the ventricular wall by one of the following methods: conventional closure of the ventriculotomy (281 patients), inverted T closure (17 patients), or endocardial patch with Dacron graft or glutaraldehyde-preserved bovine pericardium (38 patients) as illustrated in Figure 1. The inverted T closure of the ventriculotomy and the endocardial patch techniques were developed in an attempt to restore normal left ventricular geometry. We started to employ these two techniques in 1982 and in 1984, respectively.

There were 278 men and 58 women whose mean age was 55.7 years (range, 25 to 83 years). Table 1 summarizes pertinent clinical, hemodynamic, and angiographic data in these patients. All patients underwent heart catheterization and coronary arteriography before operation. Left ventricular ejection fraction was assessed by contrast ventriculography in 317 patients and by radionuclide angiography or echocardiography in 19. The LVA was anteroseptal in 321 patients and posterior in 15.

All operations were performed on cardiopulmonary bypass and mild systemic hypothermia. Aortic cross-

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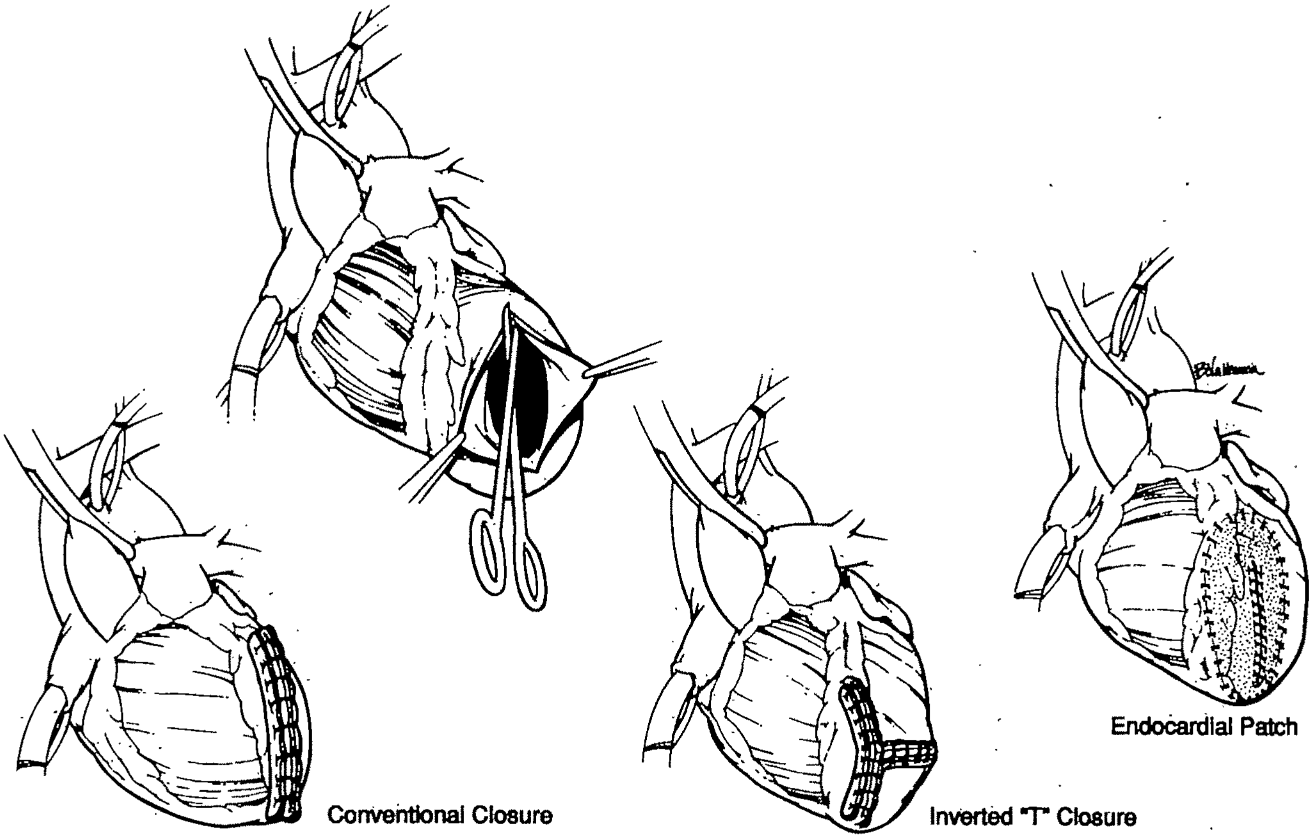

Fig 1. Operative techniques.

clamping and cold cardioplegia were employed in all patients. Crystalloid cardioplegia was used in the first 207 patients and blood cardioplegia in the last 129. Since we have begun to use blood cardioplegia, the repair of the LVA and construction of all distal and proximal anastomoses were performed with the aorta cross-clamped. When crystalloid cardioplegia was used, only the distal anastomoses were performed with the aorta cross-clamped.

At operation, 325 aneurysms were chronic and 11 were acute due to recent transmural myocardial infarction; 326 aneurysms were true aneurysms and 13 were false. Thrombus was present in 64 aneurysms. Twelve patients who had documented preoperative ventricular tachycardia or fibrillation had resection of the aneurysm without intraoperative electrophysiologic studies. All these 12 patients were operated on before 1984.

Coronary artery bypass grafts were performed in all but 17 patients. The average number of coronary arteries grafted was 2.6 per patient (range, 1 to 5). One internal mammary artery was used for grafting in 38 patients, and two arteries in 6. Endarterectomy of the right coronary artery was performed in 10 patients. In patients in whom the left anterior descending artery was ligated during repair of the LVA and the right coronary artery was totally occluded, an effort was made to bypass at least one marginal branch supplying the right ventricular wall. Bypass grafting to one marginal branch of the right coronary artery was performed in 28 patients.

The aortic cross-clamping time was 45.7 ± 18 minutes, and the cardiopulmonary bypass time was 87 ± 29 minutes.

Intraaortic balloon pump was inserted preoperatively in 27 patients because of intractable angina, heart failure, or cardiogenic shock, and postoperatively in 61 patients because of low cardiac output.

Statistical Analysis

Statistical analysis was performed with the SAS (Cary, NC) and BMDP (Los Angeles, CA) statistical programs. Clinical, hemodynamic, and angiographic data were tested to determine their value in predicting operative mortality, postoperative low cardiac output syndrome, and late mortality. Statistically significant variables were entered in a stepwise logistic regression analysis to determine their independent value. Actuarial survival curves were constructed using the Kaplan-Meier method.

Results

The operative mortality was 6.8% (23 patients). The principal cause of death was low cardiac output syndrome in 19 patients, ventricular arrhythmias in 1, stroke in 1, mesenteric artery occlusion in 1, and sepsis in 1 (Appendix Table 1A). Table 2 summarizes all serious postoperative complications.

Postoperative Low Cardiac Output Syndrome

This was the most common cause of death. A stepwise logistic regression analysis of all preoperative clinical, angiographic, and hemodynamic data indicated that the following variables were independent predictors of postoperative low cardiac output syndrome: left ventricular ejection fraction of 0.20 or less, previous myocardial revascularization, New York Heart Association functional class IV, and age greater than 60 years (Appendix Table 2A).

Operative Mortality

A stepwise logistic regression analysis indicated that left ventricular ejection fraction less than 0.20, age greater than 60 years, previous myocardial revascularization, lack of angina before operation, and New York Heart Association class IV were independent predictors of operative mortality (Appendix Table 3A).

Table 1. Clinical, Hemodynamic, and Angiographic Data in 336 Patients

Parameter	Number[a]
Previous myocardial revascularization	25 (7.4)
Angina pectoris:	
None	35 (10.4)
Stable angina	181 (53.8)
Unstable angina	120 (35.7)
Congestive heart failure	161 (47.9)
Systemic thromboembolism	18 (5.3)
Ventricular tachycardia/fibrillation	12 (3.5)
Myocardial infarction <30 days	
Subendocardial	9 (2.6)
Transmural	23 (6.8)
NYHA functional classification	
I	8 (2.3)
II	50 (14.8)
III	124 (36.9)
IV	154 (45.8)
Left ventricular end-diastolic pressure	
<25 mm Hg	201 (59.8)
>25 mm Hg	135 (40.1)
Left ventricular ejection fraction	
>0.54	3 (0.8)
0.35–0.54	44 (13.0)
0.21–0.34	140 (41.6)
<0.21	149 (44.3)
Coronary artery disease	
Left main stenosis	41 (12.2)
Triple-vessel	213 (63.3)
Double-vessel	63 (18.7)
Single-vessel	19 (5.6)
Indications for operation	
Angina pectoris	158 (47.0)
Congestive heart failure	29 (8.6)
Angina + heart failure	132 (39.2)
Other	17 (5.0)

[a] Numbers in parentheses are percentages.

NYHA = New York Heart Association.

Table 2. Postoperative Complications

Complication	Number[a]
Reexploration of the mediastinum	
For bleeding	14 (4.1)
For resuscitation	4 (1.1)
Low cardiac output syndrome	131 (38.9)
Intraaortic balloon pump[b]	61 (18.1)
Thromboembolism	
Cerebral (stroke)	11 (3.2)
Mesenteric	1 (0.3)
Arrhythmias	
Atrial fibrillation/flutter	32 (9.5)
Premature ventricular beats	114 (33.9)
Ventricular tachycardia/fibrillation	29 (8.6)
Renal failure	14 (4.1)
Respiratory failure	12 (3.5)

[a] Numbers in parentheses are percentages. [b] All because of low cardiac output syndrome.

Operative Technique

The method of repair of the LVA did not affect the overall operative mortality. However, when patients with severely impaired left ventricular function (ejection fraction of 0.20 or less) were analyzed separately, the operative mortality in those who had conventional repair was 12.6% (13 deaths among 103 patients), and in those who had inverted T closure or endocardial patch it was 6.5% (3 deaths among 46 patients). This difference was statistically significant ($p < 0.01$).

Follow-up

Patients were followed up from 1 to 13 years (mean, 6.3 years). Twenty-two patients (6.6%) were lost to follow-up. There have been 51 late deaths, 45 of which were caused by congestive heart failure, myocardial infarction, or sudden death. Cox regression analysis revealed that only left ventricular ejection fraction of 0.20 or less and left main coronary artery stenosis were independent preoperative predictors of late mortality (Appendix Table 4A). Figure 2 shows the actuarial survival of the entire group of patients. The 10-year survival was 63% ± 4%. Figure 3 shows the actuarial survival curves according to preoperative left ventricular ejection fraction, and Figure 4 shows the actuarial survival curves for patients with and without left main disease. At the latest follow-up 158 patients (66%) were in New York Heart Association class I, 50 (21%) in class II, 27 (11%) in class III, and 5 (2%) in class IV. Nine patients have suffered strokes. Eleven patients have undergone repeat myocardial revascularization.

Comment

Operation for LVA began in the late 1950s, and coronary artery bypass in the late 1960s. The addition of myocardial revascularization in patients with LVA and multivessel coronary artery disease reduced the operative mortality

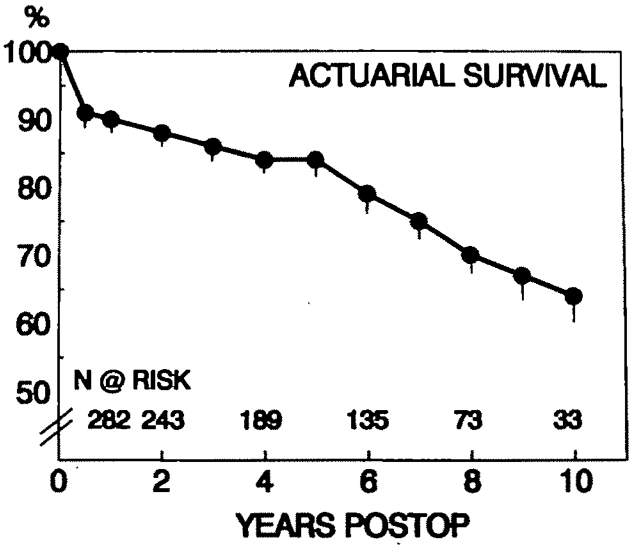

Fig 2. Overall actuarial survival of patients who had repair of left ventricular aneurysm.

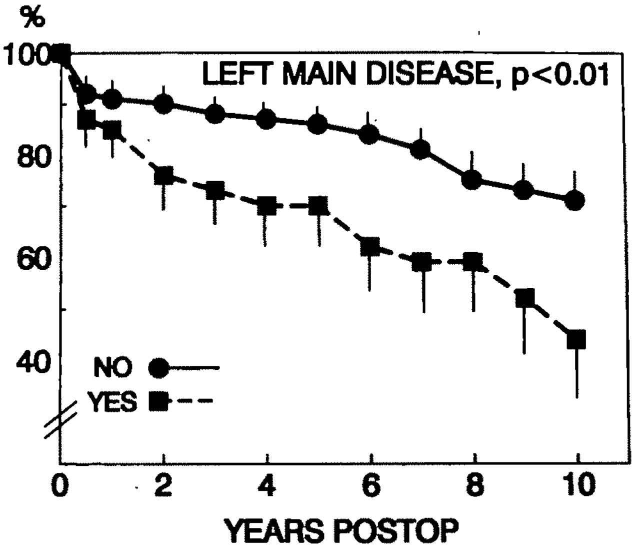

Fig 4. Effect of left main coronary artery stenosis on actuarial survival.

and increased long-term survival [4–6]. The results of operation for LVA continued to improve in the 1970s with the development of the intraaortic balloon pump and cardioplegic solutions, but by 1980 the operative mortality was yet relatively high in comparison with other cardiac operations. This fact, plus the lack of objective evidence that resection of the aneurysm improved resting left ventricular function [7], prompted many surgeons to develop alternate methods of repairing LVAs.

Jatene [3] pointed out the importance of restoring left ventricular geometry during repair of LVA to reduce operative mortality and improve long-term survival. His method of left ventricular reconstruction consisted in opening the aneurysm in the empty, beating heart and passing one or two pursestring sutures in and out of the ventricle at the transition of normal and fibrous tissue. Pulling on these sutures would restore the left ventricular cavity to its original shape. Depending on the size of the original myocardial infarction, the ventriculotomy could be closed primarily or by a Dacron patch. Jatene reported a reduction in operative mortality from 12.6% to 3.5% using this technique [3].

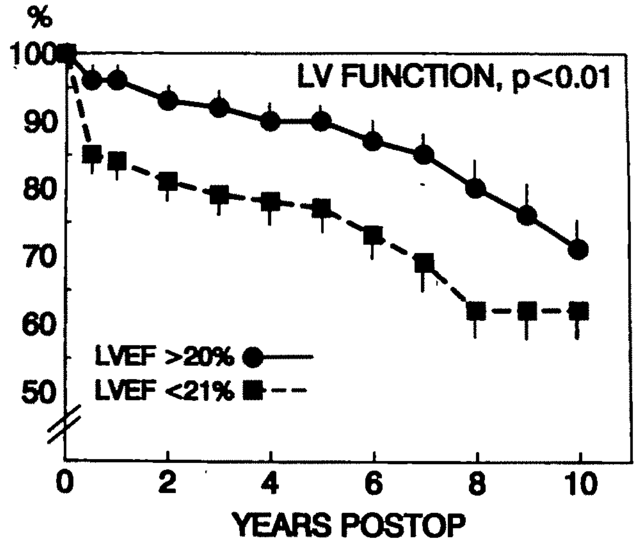

Fig 3. Effect of left ventricular (LV) function on actuarial survival.

Our attempt at restoring left ventricular geometry during repair of LVA consisted of closing the ventriculotomy in an inverted T fashion (see Fig 1). This type of closure restores the left ventricle to its conical shape. The drawback of this method of closing the ventriculotomy as well as the one described by Jatene is that they cannot be satisfactorily applied in patients with extensive fibrosis of the interventricular septum. In these cases, we believe that reconstruction of the left ventricular cavity with a Dacron patch sutured directly to the endocardium at the transition zone between scarred and viable myocardium is preferable. The size and shape of the patch should resemble those of the original myocardial infarction. This is not always easy to do in patients with chronic aneurysms because of the distortion in the anatomy of the left ventricle. It is simpler in patients with acute LVA. We prefer to use glutaraldehyde-preserved bovine pericardium to patch the endocardium in patients with acute LVA because it is easier to sew to healthy muscle than is Dacron graft.

Our data demonstrated that these newer techniques of repair of LVA are valuable in patients with severely impaired left ventricular function. The operative mortality was reduced from 12.6% when conventional repair was used to 6.5% when inverted T closure or endocardial patch was used. The endocardial patch technique is also valuable in patients with acute aneurysms who need operation because of shock or intractable heart failure. We had no operative deaths among 8 patients with acute LVA who were treated by this method. We have also used this technique in patients with postinfarction ventricular septal defect with most impressive results [8]. This newer technique of repair of LVA does not seem to be important in patients with only moderate impairment of left ventricular function.

The impairment of left ventricular function in patients with LVA may be due to distortion of left ventricular geometry by the aneurysm or by fibrosis of other segments of the ventricular wall due to extensive coronary artery disease [3, 6, 9]. The importance of complete revascularization should not be overlooked [5, 6, 9]. We believe that this should include bypassing the proximal third of the left anterior descending artery or the first septal perforator branch if the proximal part of the septum is found not to be scarred at operation. Another detail during revascularization is that the distal half of the anterior descending artery is often ligated during closure of the ventriculotomy [4], and it may have been the principal source of collaterals to the marginal branches of an occluded right coronary artery. Although postoperative right ventricular dysfunction is common after repair of LVA [10], it can be an extremely serious [11] and sometimes fatal complication. We believe that at least one marginal branch of the right coronary artery should be bypassed in this subset of patients with LVA.

A stepwise logistic regression analysis of multiple clinical, hemodynamic, and angiographic variables in our patients identified poor left ventricular function, age greater than 60 years, previous myocardial infarction, lack of angina pectoris, and New York Heart Association functional class IV as independent predictors of operative mortality. Other investigators have come to similar conclusions [12–15]. Repair of LVA alone should not be performed in patients with ventricular tachycardia or fibrillation. Early in our experience we had a high mortality in this group of patients. The operative risk is decreased by intraoperative electrophysiologic mapping to guide resection or ablation of the arrhythmogenic focus [16, 17].

The long-term survival after repair of LVA in our series is comparable with that of other reports [6, 13]. Most investigators have identified poor left ventricular function as an important predictor of late mortality [9, 13–15]. The 10-year actuarial survival in our patients with moderate impairment of left ventricular function was 71% ± 7%; for patients with severe impairment it was 61% ± 6%. This difference in long-term survival was statistically significant. Patients with poor left ventricular function usually have symptoms of congestive heart failure before operation. Thus, heart failure has also been identified as a predictor of late mortality [6, 9, 13]. The best long-term results were obtained in patients who were operated on primarily for angina pectoris [6, 9, 13, 15]. In our series the presence of left main coronary artery stenosis was also a predictor of late mortality after repair of LVA.

Our data indicate good long-term results after repair of LVA. Techniques aimed to restore normal left ventricular geometry have a favorable effect in operative mortality in patients with poor left ventricular function. They may also improve long-term survival.

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Appendix

Table 1A. Operative Mortality in Various Subsets of Patients With Left Ventricular Aneurysm

Variable	No. of Patients	No. of Deaths[a]	p Value[b]
Sex			0.246
Male	278	17 (6.1)	
Female	52	6 (10.3)	
Age			0.060
60 y or less	221	11 (5.0)	
>60 y	115	12 (10.4)	
Previous myocardial revascularization			0.048
Yes	26	4 (15.3)	
No	339	19 (5.6)	
Angina pectoris			0.183
None	35	5 (14.3)	
Stable	181	11 (6.1)	
Unstable	113	7 (5.3)	
NYHA functional class			0.042
I	8	0 (0)	
II	53	1 (1.9)	
III	138	5 (3.6)	
IV	165	17 (10.2)	
Acute myocardial infarction			0.174
None	298	19 (6.4)	
Subendocardial	9	2 (22.2)	
Transmural	23	2 (8.7)	
Preoperative embolism			0.461
No	318	21 (6.6)	
Yes	18	2 (11.1)	
LV ejection fraction			0.010
>0.20	195	7 (3.6)	
<0.21	152	16 (10.5)	
Preop ventricular tachycardia[c]			0.000
Yes	12	6 (50)	
No	353	17 (4.8)	
Predominant symptoms			0.000
Angina alone	158	4 (2.5)	
Angina + CHF	132	10 (7.6)	
CHF alone	29	3 (10.3)	
Multiple	17	6 (35.3)	
Coronary artery disease			0.207
One-vessel	19	0 (0)	
Two-vessel	56	7 (11.1)	
Three-vessel	246	16 (6.5)	
Left main disease			0.167
Yes	41	5 (12.2)	
No	285	18 (6.3)	
Number of occluded coronary arteries			0.281
None	40	9 (0)	
One	189	15 (7.9)	
Two	81	7 (8.6)	
Three	7	1 (12.5)	
Thrombus in the aneurysm			0.025
Yes	61	8 (13.1)	
No	275	15 (5.5)	
Right coronary endarterectomy			0.101
Yes	10	2 (20)	
No	319	21 (6.6)	
Location of aneurysm			0.538
Anteroseptal	321	21 (6.5)	
Posterior	15	2 (13.3)	
Pathology of aneurysm			0.662
Acute	11	1 (9.0)	
Chronic	325	21 (6.4)	
Method of repair			0.954
Conventional	281	19 (6.8)	
Inverted T closure	17	1 (5.9)	
Endocardial patch	38	2 (7.9)	
Aortic cross-clamping:			0.015
≤50 min	221	8 (3.6)	
>50 min	143	15 (10.5)	
Postop low output syndrome			0.000
Yes	137	20 (14.6)	
No	225	3 (1.3)	

[a] Numbers in parentheses are percentages. [b] The p values were calculated by univariate analysis. [c] Not entered into stepwise logistic regression analysis (no cases operated on since 1984).

CHF = congestive heart failure; LV = left ventricular; NYHA = New York Heart Association.

Table 2A. Low Cardiac Output Syndrome: Results of Stepwise Logistic Regression Analysis

Variable	χ^2	p Value
Left ventricular ejection fraction <0.21	28,201	0.000
Previous myocardial revascularization	13,994	0.000
NYHA functional class IV	12,406	0.000
Age > 60 years	6,242	0.012

NYHA = New York Heart Association.

Table 3A. Operative Mortality: Stepwise Logistic Regression Analysis^a

Variable	χ^2	p Value
Left ventricular ejection fraction <0.21	5,280	0.022
Age > 60 years	3,712	0.054
Previous myocardial revascularization	3,374	0.064
Lack of angina pectoris	3,374	0.066
NYHA functional class IV	3,053	0.081

^{a} $p < 0.1$ is considered significant.

NYHA = New York Heart Association.

Table 4A. Late Mortality: Stepwise Logistic Regression Analysis

Variable	χ^2	p Value
Left ventricular ejection fraction <0.20	8,207	0.004
Left main coronary artery stenosis	8,022	0.005

DISCUSSION

DR WILLIAM S. STONEY, JR (Nashville, TN): I congratulate Dr Komeda and his associates on a fine presentation, and also for their excellent results. They have correctly placed emphasis on ventricular aneurysm repair rather than simple excision, and attribute a reduced overall mortality in high-risk patients to this type of repair. I would agree with this conclusion, with the reservation that some part of the reduced mortality could be attributed to better myocardial protection and other advances and improvements in the conduct of cardiac surgical procedures.

I would like to make a point about ejection fraction. The ejection fraction is the standard gauge of operative risk for most cardiac operations. In patients with very large ventricular aneurysms, the ejection fraction will be quite low, suggesting high risk, but if the nonaneurysmal portion of the ventricle contracts well, the operative risk actually can be quite reasonable. Therefore, we, like others, have tried to evaluate risk by looking at the function of the nonaneurysmal portion of the left ventricle.

We divided our patients into three groups: those patients with good function of the nonaneurysmal portion of the left ventricle, those with very poor function of the nonaneurysmal left ventricle with one akinetic segment, and those in between with impaired function. Those patients with really good contractility had a low hospital mortality: those with some impairment had a higher operative mortality; and those with an akinetic segment and very poor function had a high operative mortality and a high late mortality. At the present time, we do not recommend aneurysm repair on this third group of patients. When the nonaneurysmal portion of the ventricle contracts well, you can expect the patient to do well and not to have a high operative risk, even if the overall ejection fraction is low.

Finally, I would like to ask one question. Pericardial patches have been used for many years in the right ventricle. Dr Komeda, do you think there is a risk for late aneurysmal formation or other problems with pericardial patches in the left ventricle?

DR LAWRENCE I. BONCHEK (Lancaster, PA): This has been another very insightful report from the Toronto group under Tirone David's leadership, and it prompted me to review our much more recent experience to assess the importance of patch repair of left ventricular aneurysms.

Beginning in 1983 in Lancaster, we had experience with 89 patients if we exclude those, as Komeda and associates did, with ventricular septal defects, as well as those who had mapping, endocardial resection, and cryoablation. If we added back those 20 patients, it would bring another death into this series. Eighty-six of the patients had associated coronary bypass. There were two mitral valve replacements.

There was one death in 89 patients. We define inotropic support very stringently. Any patient who leaves the operating room with inotropic support is counted as having received inotropic support. We do not use a 12-hour or 24-hour criterion. Thirty-five percent (31 patients) received inotropic support, and 5.6% of patients had a new intraaortic balloon pump inserted postoperatively.

We believe that myocardial protection is very important, and we generally try to provide optimal myocardial protection, which to us means not clamping the aorta. In 84 of the 89 patients we did not clamp the aorta while operating on the aneurysm, and in 13 patients we did not clamp the aorta at all, even while doing the coronary bypass grafts. Only 6 patients received blood cardioplegia, usually because of substantial aortic regurgitation. We closed the aneurysm directly in 85 patients. We occasionally will just plicate even a large aneurysm if the echocardiogram raises no concern about thrombus and there is some aortic regurgitation, and also we can thereby avoid any concern about air. We did use patch closure in only 4 patients.

So the results of this experience, to us, suggested that myocardial protection is crucial, and that patch closure has a role to play, but it is by no means necessary in a large number of patients. The point I wish to make is that a discipline as complex as cardiac surgery advances on many fronts, and results of operation are constantly improving. I would caution against concluding that a particular method of repair of left ventricular aneurysms is the reason for improved results and is necessary or even suitable for all patients.

I have two specific questions. Your review was a retrospective one. In which patients now do you select a nonconventional closure of the aneurysm? And second, how did you calculate ejection fraction? As Dr Stoney pointed out, the asymmetry imposed by an aneurysm invalidates the Dodge formula that is used to calculate a three-dimensional ejection fraction from the two-dimensional angiogram.

DR L. HENRY EDMUNDS, JR (Philadelphia, PA): I also compliment Dr Komeda and associates for a nice series. Dr Ed Savage and his colleagues at the University of Pennsylvania studied the effect of aneurysmal plication on left ventricular mechanics. To do this they used a sheep apical aneurysm model and a new technique of ventricular imaging called two-dimensional sonomicrometry imaging, which was developed by Dr Mark Ratcliffe and his colleagues.

In this technique, nine sonomicrometry crystals are placed on the epicardial surface in the midsagittal plane, and endocardial crystals are placed beneath six of the epicardial crystals. Using this technique, the epicardial and endocardial contours of the ventricle are continuously imaged throughout the cardiac cycle. Assuming an axis of symmetry, which does not change after plication, and using Janz equations, regional wall stresses and strains in various sections of the myocardial wall can be calculated. Dr Savage found that plication does not change hemodynamics; neither cardiac output nor various chamber pressures change significantly.

However, the change in geometry fails to decrease anterior wall stress but does decrease posterior wall stress. It increases end-systolic elastance, which is a measure of contractility, but after plication this increase is due to a loss of diastolic compliance. There is no net increase in the force of contractility.

Using this and related technology, we believe that it will be possible to develop superior operations for left ventricular aneurysm. Possibilities include the Dor operation, or endocardial patch, and operations involving skeletal muscle cardiomyoplasty.

DR DENTON A. COOLEY (Houston, TX): I too enjoyed this excellent paper from Toronto. We first reported repair of postinfarction ventricular aneurysm with cardiopulmonary bypass 30 years ago. At that time, we adopted the same concept of excision and lateral repair that was used to repair sacciform aortic aneurysms. It seems that our minds were closed to changes in technique from that point forward, however, until just recently. After some 2,500 cases of ventricular aneurysm, we modified the technique and now repair the aneurysm internally by using a patch graft.

We call this technique endoaneurysmorrhaphy, a term that Dr Rudolph Matas coined more than a century ago. No external or epicardial foreign bodies are applied in this repair. We are careful not to interfere with the left anterior descending coronary artery or the interventricular groove. We have found almost routinely that we can revascularize that essential artery with an internal mammary artery. Several surgeons, including Dor, Jatene, Komeda and associates, and ourselves, now use similar techniques. The drawings in this report by Komeda and associates reveal closure of the anterior descending artery by the repair, particularly the inverted T repair. I believe this to be improper. We should try to preserve the epicardium and, especially, the left anterior descending coronary artery at all costs.

During the past 2 years, we have used left ventricular endoaneurysmorrhaphy in 91 patients. Seven patients have died. A number of these patients were sent to us for cardiac transplantation. I must confess that we attempted this technique even though some of these patients had rather diffuse myocardiopathy rather than a localized aneurysm. Functional results, however, have been exceptionally good when compared with results obtained by former techniques.

Recently one of my colleagues, Dr Zvonimir Krajcer, reviewed our cases to determine whether postoperative ventricular function was better in patients who underwent endoaneurysmorrhaphy than in patients who underwent conventional repair. Dr Krajcer determined that the ejection fraction averaged 0.05 better, which was not particularly striking. The ejection fraction was better, however, in a comparable series of more advanced cases done by conventional repair.

In 1 patient, for example, nuclear ventriculograms using technetium revealed a striking improvement in ejection fraction (more than a twofold increase) in diastole and systole after left ventricular endoaneurysmorrhaphy.

The technique can be adapted easily to repair lesions resulting from acute infarction, ventricular septal defect, and even cardiac rupture.

DR C. E. ANAGNOSTOPOULOS (Stony Brook, NY): I echo the first two discussants', Dr Stoney's and Dr Bonchek's, general concerns, and in an effort to quantify the mystery of ejection fraction as a predictor in left ventricular aneurysms, I would like to remind Komeda and associates of a study by Kapelanski, Al-Sadir, and others that was published in *Circulation* just about the time their studies started. That study showed that regardless of overall ejection fraction, results, particularly in emergency aneurysms, were more related to the baseline, nonaneurysmal ejection fraction even if it was down to 0.30.

My question is, did they or could they analyze this baseline nonaneurysmal ejection fraction in the survivors versus the nonsurvivors in the high-risk group, and is it possible that this, rather than improved preservation or cardioplegia technique, is the reason for the excellent results?

DR DAVID: I would like to thank all the discussants. Dr Stoney and other discussants mentioned the problems in using global ejection fraction in patients with left ventricular aneurysm to assess operative risk, and we agree entirely. Segmental wall motion analysis, particularly of the basoconstrictor muscles, is more important than global ejection fraction in these patients. Unfortunately, our study was a retrospective one, and the preoperative data were collected from a computer databank where only global ejection fraction was recorded. Dr Komeda has promised us to review all preoperative angiograms to assess the relationships between preoperative segmental wall motion, global ejection fraction, and operative outcome.

Although we have used autologous pericardium to repair postinfarction ventricular septal defect and acute left ventricular aneurysm in numerous patients without a single case of patch aneurysm, we prefer glutaraldehyde-preserved bovine pericardium because it is readily available and easier to handle. We use Dacron graft in patients with chronic left ventricular aneurysms.

I have to congratulate Dr Bonchek for his outstanding results. I do not believe that the technique of myocardial protection you used is responsible for your results. I also close the ventriculotomy primarily in patients with small aneurysms. We use the endocardial patch technique in patients with large ventricular aneurysms and in those with impaired left ventricular function. In these patients, we believe that a repair that aims at restoration of left ventricular geometry will have a favorable effect on the surgical outcome. We have studied left ventricular function by pressure–volume relationships in a small number of patients before and after operation and found better systolic function in patients who had repair using these newer operative techniques.

We agree with Dr Edmunds' remarks. Those types of experiments will allow us to determine the best method of repair.

Dr Cooley, I am not certain that the left anterior descending artery has to be saved in all patients with ventricular aneurysm. If the proximal part of the interventricular septum is not scarred and the anterior descending coronary artery is occluded at its origin, it may be important to bypass its proximal third or the first septal perforator. In other cases, the anterior descending artery may be the principal source of collaterals to occluded marginal branches of the right coronary artery, and ligation of the anterior descending without grafting the marginal branches may result in right ventricular infarction. In most patients, however, ligation of the distal half of this artery does not seem to cause any harm.

Evaluation of an Extraaortic Counterpulsation Device in Severe Cardiac Failure

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A valveless, single-orifice polyurethane ventricle with a maximum stroke volume of 60 mL was implanted on the brachiocephalic artery just above the aortic arch in sheep ($n = 14$) to act as an extraaortic counterpulsation device. In parallel, an intraaortic balloon was placed in the descending thoracic aorta. Both devices were pneumatically driven with an intraaortic balloon pump console that was gated by the electrocardiogram to provide aortic diastolic augmentation at a stroke volume of 40 mL. To compare the efficacy of counterpulsation for each device during severe cardiac failure, biventricular block was induced by continuous infusion of esmolol (100 to 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$), titrated to reduce aortic flow and pressure to less than 75% of baseline. Pulsatile coronary and aortic flows were recorded with ultrasonic flow probes placed around their respective vessels. Aortic root and left ventricular pressures were recorded using micromanometers. The enhancement of hemodynamic variables for both devices were compared for optimal timing conditions, which were defined as inflation set just before the dicrotic notch and deflation bordering on isovolumetric systole. The extraaortic counterpulsation device was able to significantly augment aortic and coronary flows while simultaneously decreasing left ventricular tension time index and aortic end-diastolic pressure ($p < 0.02$). The intraarotic balloon pump was able to significantly reduce only tension time index ($p < 0.002$) to a lesser extent that the extraaortic counterpulsation device. All analysis was performed with the paired-samples *t* test. The extraaortic counterpulsation device greatly improves the myocardial oxygen supply-consumption ratio of the left ventricle by increasing diastolic coronary flow and reducing left ventricular wall tension during systole. The salutary effects of the extraaortic counterpulsation device greatly exceed those of the intraaortic balloon pump, and it may, therefore, provide a viable alternative for patients in pump failure after cardiopulmonary bypass.

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Cardiac assist devices are used in the preoperative and postoperative care of patients undergoing cardiac operations [1, 2] or as bridges for patients awaiting cardiac transplantation. Patients with compromised ventricular function may benefit from drug therapy using digitalis, diuretics, or inotropic agents [3]. If such interventions fail, the only remaining therapy that can be offered is mechanical circulatory support, most commonly provided by the intraaortic balloon pump (IABP). Balloon counterpulsation decreases afterload and therefore myocardial oxygen consumption by the reduction of aortic end-diastolic pressure (EDP) and tension time index (TTI). It improves systemic blood pressure (despite decreased left ventricular pressure) by increasing mean diastolic pressure, which improves myocardial perfusion through the coronary circulation. The overall result is the improvement of the myocardial oxygen supply–consumption ratio of the left ventricle (LV) [2]. Intraaortic balloons (IAB) are also easily placed by percutaneous insertion through the femoral artery. Considerable experience has been obtained with the use of the IABP in the management of patients with coronary artery disease [4–8], but with much less frequency over extended periods of time while a patient is awaiting cardiac transplantation. The IABP is not without serious vascular complications and potential morbidity and mortality [9, 10]. These complications tend to be exacerbated with prolonged support times. Additionally, the IABP can require that the patient remain bedfast in a supine position, which may further reduce his or her strength and stamina.

The major drawback of the IABP is its ineffectiveness in severe cardiac failure when systolic aortic pressure drops to less than 70 mm Hg [11, 12]. This is because IABP counterpulsation produces its hemodynamic effects by altering the aortic input impedance presented to the LV. Hence, increases in aortic flow that result from institution of IABP must be supplied directly by LV output, which is markedly limited in severe cardiac failure. Additionally, the balloon's presence in the aorta presents an impedance to blood flow during inflation and deflation, which can actually increase afterload if the IABP is not carefully

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synchronized to deflate before systole [13]. Finally, the distal placement of the balloon in the descending aorta relative to the aortic valve can diminish the pressure pulse created during diastole [14].

In severe cardiac failure, left ventricular assist devices are commonly used because they bypass the LV and can receive blood from cannulation of either the left atrium or the apex of the left ventricle [15]. Several types of left ventricular assist devices are available that use some variation of standard artificial heart chamber technology. Left ventricular assist devices produce extraaortic counterpulsation directly above the aortic valve by supplying a fixed stroke volume directly into the aorta. The proximal location increases the efficacy of counterpulsation; and the absence of the device in the aorta reduces some of the timing and impedance problems associated with the IABP. Although left ventricular assist devices are capable of supplying a large percentage of total cardiac output, implantation can be difficult and usually requires cardiopulmonary bypass.

The idea of extraaortic counterpulsation is not new, and extraaortic counterpulsation has been shown previously to be an effective modality of cardiac assistance. Nose and associates [16] originally demonstrated that a small (20 mL), single-orifice Silastic chamber anastomosed to the aorta provided maximum hemodynamic augmentation when placed as close as possible to the aortic valve. A similar concept was used by Bregman [17] to augment hemodynamics with a compliant chamber in conjunction with an IABP. Gabbay and Frater [18] demonstrated that a much larger device (100 mL) could provide dramatic effects for mongrel dogs in cardiac failure. Nanas and colleagues [19, 20] demonstrated that a smaller device (80 mL) could provide significant augmentation when implanted in the ascending aorta in severe cardiogenic shock.

The purpose of this investigation was to develop a device that would address a clinical audience in which IABP is ineffective. In particular, the device could be used in patients in whom insertion of an IAB is not possible, to wean patients from cardiopulmonary bypass or balloon dependency and possibly serve as a bridge for patients awaiting cardiac transplantation. The design criteria were high efficiency, ease of implantation, maximum biocompatibility, and low cost. To satisfy these goals, a single-orifice, valveless, polyurethane artificial ventricle with a maximum stroke volume of 60 mL was fabricated for use as an extraaortic counterpulsation device (EACD). The polyurethane components of the ventricle were vacuum-formed on simple molds and joined together with radiofrequency welding [21]. This produces a smooth, flexible ventricular cavity that is highly biocompatible, easy to manipulate, and inexpensive to fabricate and can be pneumatically driven with conventional IABP consoles. This combination of a flexible polyurethane architecture and small size also facilitates device implantation. The single-orifice valveless configuration eliminates potential blood trauma due to the presence of valve leaflets in the device. To evaluate the effectiveness of this new EACD, the device was implanted on the aortic arch of sheep in severe biventricular failure and its hemodynamic effects were compared with those of the IABP for identical stroke volumes.

Material and Methods

To compare the efficacy of counterpulsation for the EACD versus the IABP, experiments were performed on 14 Suffolk sheep ranging from 50 to 60 kg in weight. After a 48-hour fast and overnight abstinence from water, all animals were preoperatively sedated with an intramuscular injection of ketamine (10 mg/kg). General anesthesia was induced by intravenous pentobarbital (25 to 30 mg/kg). The animals were intubated, mechanically ventilated, and maintained with inhalation anesthesia (oxygen 50%, isoflurane, 1.0% to 1.5%). Body temperature was maintained at 37°C with a recirculating water blanket. The electrocardiogram was continuously monitored.

Bilateral groin cut-downs were performed to gain access to the femoral vessels. A 7F micromanometer (PC-350; Millar Instruments, Houston, TX) catheter was placed through a femoral artery into the ascending aorta. A 7F Swan-Ganz catheter was placed through the ipsilateral femoral vein into the main pulmonary arterial trunk. An adult 40-mL IAB was placed into the thoracic descending aorta through the contralateral femoral artery. The animal was heparinized with 400 U/kg.

The heart was approached through a median sternotomy in the usual fashion and the heart was suspended in a pericardial cradle. Instruments were inserted into the animal as diagrammed in Figure 1. A 20-mm transit time ultrasonic flow probe (Transonics Systems Inc, Ithaca, New York) was placed around the aortic root. Another 20-mm ultrasonic flow probe (Transonics) was placed around the aortic arch just distal to the brachiocephalic artery. The combination of both probes allowed calculation of aortic root flow, EACD flow, and net systemic flow. A 4-mm ultrasonic flow probe (Transonics) was placed around the left main coronary artery after sharp dissection through the epicardial fat pad. A 5F micromanometer (Millar PC-350) was placed into the LV cavity through an apical stab wound and secured by a 2-0 silk pursestring.

The brachiocephalic artery was isolated and occluded with a vascular clamp proximally, and tied off with a 1-0 silk suture distally. It was then transected and an end to end anastomosis was created between the brachiocephalic artery and the Dacron graft of the EACD with a continuous 4-0 polypropylene stitch. The anastomosis was placed close to the aorta. The vascular clamp was then intermittently released to fill the EACD with blood, and air was vented with a 25-gauge needle through the Dacron graft.

Severe biventricular failure was then induced using esmolol (100 to 600 $\mu g \cdot kg^{-1} \cdot min^{-1}$) titrated to reduce aortic flow to less than 75% of baseline. Esmolol was delivered at a constant rate by an infusion pump (Lifecare, model 4P; Abbott Labs, North Chicago, IL) adjusted to ensure that all preparations had a average heart rate of 100 beats/min.

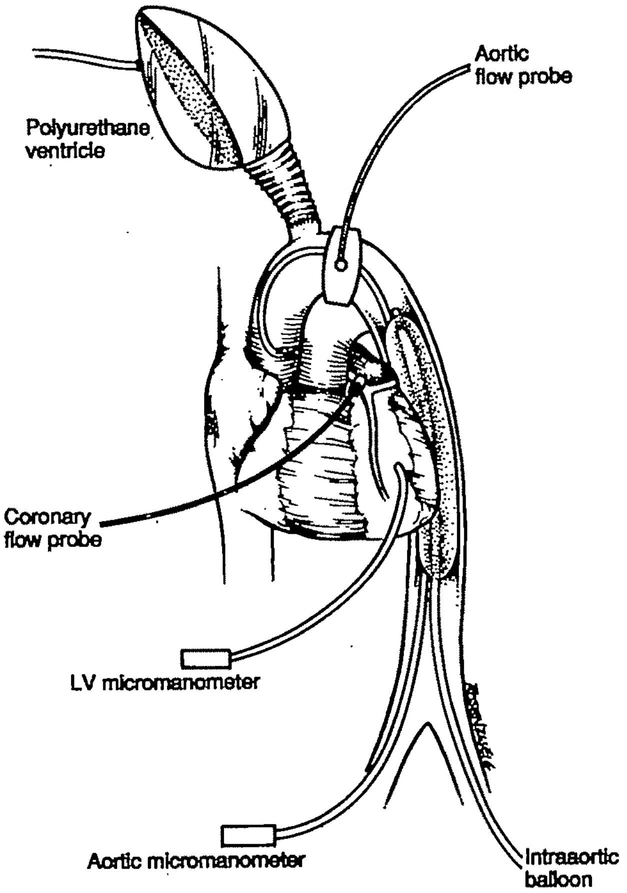

Fig 1. Experimental setup showing placement of ultrasonic flow transducer, micromanometer pressure transducers, intraaortic balloon pump, and extraaortic counterpulsation device. For detailed explanation, see Material and Methods section. (LV = *left ventricular.)*

The pneumatic chamber of the EACD and the IAB were both driven with helium gas by a conventional IABP control console (System 83; Datascope, Paramus, NJ) with fill volumes set to 40 mL. The electrocardiogram, pulsatile aortic and coronary flows, pulmonary arterial pressure, aortic pressure, and left ventricular pressure were continuously monitored on a multichannel preamplification and display system (Honeywell, New York, NY). The solenoid timing signal from the IABP control console was also monitored by the data acquisition system. Inflation and deflation were indicated by the solenoid timing signal, which controls the pressure and vacuum into the assist device. If the solenoid signal is high, the assist chamber is pressurized. A low signal indicates that a vacuum is applied to the chamber. Except for solenoid timing, all signals were low-pass filtered and fed to a custom-built personal computer–based data acquisition system used for acquisition, storage, and analysis of data. The sampling rate for data acquisition was 200 Hz.

All data acquisition runs were 30 seconds in length. The first 10 seconds were used to collect control data and the final 20 seconds were used to acquire data during cardiac assistance. At least 1 minute was allowed between data acquisition runs to allow the cardiovascular system to stabilize in the absence of cardiac assistance. Baseline hemodynamic data before esmolol infusion were collected after all operative procedures were completed. The timing of counterpulsation for both devices was varied under computer control to precisely determine the times of inflation and deflation relative to the electrocardiographic R wave for each beat. Optimal inflation was determined by initially setting inflation to be coincident with the second heart sound and adjusting timing slightly earlier to smoothly obliterate the notch without causing any distortion of the systolic pressure peak. Optimal deflation was initiated at the electrocardiographic P wave and moved later in diastole so as to yield minimum aortic EDP. This point was usually defined as the border of isovolumetric systole. Late deflation was defined as any deflation timed later than optimal deflation that yields increased aortic EDP. The present study focuses on optimal timing and late deflation only; however, during each experiment an extended series of timing runs for both early inflation and late deflation were performed for both devices, in 5-millisecond increments starting from their optimum points to obtain the complete timing dependence of both devices. In each experiment, 200 to 300 runs were collected.

The derived quantities calculated from the observed hemodynamic parameters were TTI (the integral of left ventricular pressure over systole, used as an indirect measure of myocardial oxygen consumption), total coronary flow, total aortic flow, and aortic EDP. Although TTI can be rate dependent, we maintained the average heart rate at 100 beats/min for all preparations as described above. The quantities were determined for unassisted conditions and during counterpulsation obtained with each device. Percentage changes between assisted and unassisted conditions for both devices were calculated for all hemodynamic variables using the customized data analysis program. Group averages ± standard errors were calculated for all animals in the study. Statistical analysis was performed on the means using the paired-samples *t* test to assess the significance of the changes in the hemodynamic variables observed.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Table 1 summarizes the observed changes in hemodynamic variable obtained during IABP use. Baseline values are shown before esmolol infusion to demonstrate the level of LV failure present in the preparation. It is evident that for optimal timing conditions during cardiac failure, only the average change in TTI was significant ($p < 0.002$). The augmentation of coronary flow approached significance ($p < 0.085$) with an average change of less than 15%. Changes in EDP and aortic flow were both small and of no statistical significance. These results indicate that there is a small degree of afterload reduction of the left ventricle during IABP use in severe cardiac failure and some marginal changes in coronary flow. In general, the hemodynamic effects obtained with the IABP under these conditions were not impressive.

Table 1. Hemodynamic Effects of Intraaortic Balloon Pumping

Measurement	TTI	Q_A	Q_C	AoEDP
Baseline	30.6 ± 2.8	2299 ± 247	136.9 ± 23.9	71.9 ± 7.7
Ventricular failure				
Unassisted	26.6 ± 2.5	1202 ± 159	78.1 ± 16.1	54.4 ± 6.4
Assisted	25.2 ± 2.0	1238 ± 188	88.2 ± 19.8	55.1 ± 5.6
% Change	−5.2	2.9	12.9	1.2
p Value[a]	0.0019	0.390	0.084	0.695

[a] *p* values determined by the paired-samples *t* test.

AoEDP = end-diastolic pressure (mm Hg); Q_A = total aortic flow (mL/min); Q_C = total coronary flow (mL/min); TTI = tension time index (mm Hg · s).

Table 2 summarizes changes in hemodynamics for the EACD. In contrast to the IABP, the changes in all hemodynamic variables were significant. Both TTI and aortic EDP were decreased significantly ($p < 0.0001$) with percentage changes far exceeding those obtained with the IABP. Aortic and coronary flows were both significantly increased by more than 20%, yielding greater augmentation than the IABP. It is important to note that although the absolute changes in aortic flow and EDP are not large enough to maintain adequate systemic perfusion, ionotropic agents would be used in conjunction with cardiac assistance to produce adequate changes clinically. In general the results indicate that counterpulsation instituted using the EACD yielded far greater hemodynamic benefits when compared with the IABP for severe cardiac failure in both the magnitude and significance of the observed changes.

Representative tracings of hemodynamic data are used to illustrate the salient changes during EACD and IABP. Figure 2 shows solenoid, pressure, and flow waveforms for counterpulsation obtained with the EACD for optimal timing conditions. The unassisted data for aortic and LV pressures appear normal in shape and phasing. The low peak values of these pressures (approximately 66 mm Hg) indicate severe heart failure. Although the filtering of aortic pressure has removed some of the higher frequency components of the second heart sound, the inflection of the waveform at end-systole is readily apparent. Upon initiation of cardiac assistance using the EACD, optimal inflation occurs just before the second heart sound as indicated from the solenoid timing. This results in a increase in aortic diastolic pressure, which is caused by the chamber ejecting its stroke volume into the aorta. This pressure augmentation is maintained until the onset of isovolumetric systole when a vacuum is applied to the chamber. This causes a rapid filling of the chamber while the ventricle is starting its ejection into the aorta. The volume displacement due to the filling of the EACD causes a decrease in both LV and aortic EDP. Hence, afterload has been substantially reduced by this device due to the vacuum effect of the device in early systole.

Table 2. Hemodynamic Effects of the Extraaortic Counterpulsation Device

Measurement	TTI	Q_A	Q_C	AoEDP
Baseline	30.6 ± 2.8	2299 ± 247	136.9 ± 23.9	71.9 ± 7.7
Ventricular failure				
Unassisted	26.3 ± 2.3	1235 ± 136	85.9 ± 17.6	53.1 ± 6.4
Assisted	22.3 ± 2.0	1601 ± 174	106.8 ± 21.5	47.0 ± 5.9
% Change	−15.1	29.6	24.4	−11.5
p Value[a]	0.0001	0.017	0.008	0.0001

[a] *p* values determined by the paired-samples *t* test.

AoEDP = end-diastolic pressure (mm Hg); Q_A = total aortic flow (mL/min); Q_C = total coronary flow (mL/min); TTI = tension time index (mm Hg · s).

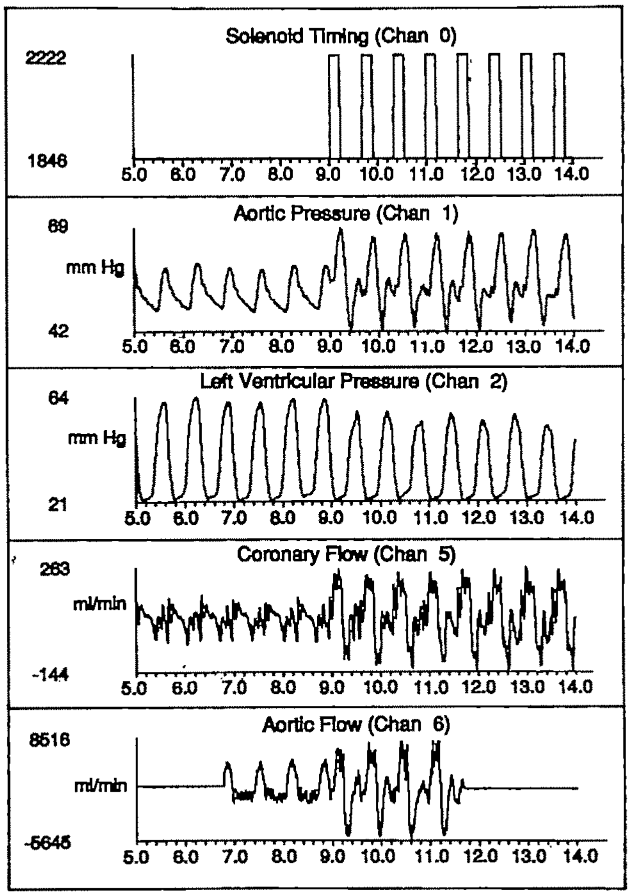

Fig 2. Solenoid timing, aortic pressure, left ventricular pressure, total coronary flow, and aortic flow waveforms versus time in seconds for counterpulsation using the extraaortic counterpulsation device when set for optimal timing conditions. Pressure is in millimeters of mercury; flow is in milliliters per second. All counterpulsation was performed during cardiac failure.

The effects of the EACD on coronary and aortic flows are also apparent. For unassisted conditions, the waveforms have their normal shapes and phases when compared with aortic pressure. During EACD assistance, an increase in peak and total coronary flow occurs that coincides with the increase in aortic diastolic pressure. The aortic flow wave is obtained from the flow probe located distal to the brachiocephalic artery. In the absence of cardiac assistance, this waveform has close to a zero baseline and has its typical peak in systole. During assis-

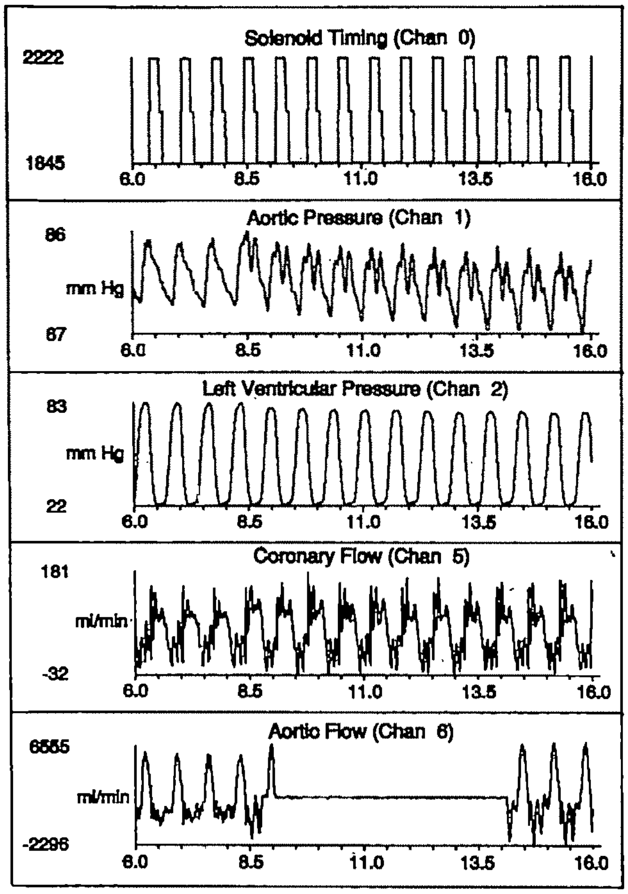

Fig 3. Solenoid timing, aortic pressure, left ventricular pressure, total coronary flow, and aortic flow waveforms versus time in seconds for counterpulsation using the intraaortic balloon pump when set for optimal timing conditions. Pressure is in millimeters of mercury; flow is in milliliters per second. All counterpulsation was performed during cardiac failure.

tance, an increase in total flow occurs; however, the waveform is now biphasic due to a proportionally higher percentage of flow occurring in diastole. This is because the EACD can physically pump blood and is ejecting its stroke volume into the aorta. At the end of diastole, a vacuum is applied to the IABP console chamber to begin the filling phase of the EACD. The filling of the EACD causes negative transitions in the aortic flow wave for a fraction of a second at the onset of systole which are subsequently eliminated as LV ejection begins.

Figure 3 shows solenoid, pressure and flow waveforms during IABP counterpulsation set for optimal timing conditions. As in Figure 2, all unassisted waveforms have their normal shape and phase. During cardiac assistance, similar changes are observed with the IABP as with the EACD; however, the magnitudes of the changes are less. The decrease in LV pressure is smaller than that obtained with the EACD. Aortic EDP is reduced by a few percent indicating that the total afterload reduction obtained with the IABP in severe heart failure is less than the reduction observed during EACD assistance. There is a reasonable increase in mean aortic diastolic pressure, which gives rise to a noticeable increase in coronary flow. Aortic flow obtained during IABP is increased by a small amount owing to afterload reduction; however, the waveform is not biphasic in nature. The IABP simply causes a volume displacement within the aortic cavity that modulates the afterload presented to the left ventricle. The IABP cannot physically pump blood and will not produce blood flow during diastole, which prevents the formation of a biphasic flow wave.

Figure 4 shows the effects of EACD for late deflation timing. From the solenoid timing, it is clear that deflation is initiated during the early ejection phase of systole. In spite of this, afterload reduction still occurs as indicated by the decrease in peak values of LV pressure. The only detrimental effect of late deflation timing using the EACD is an increase in aortic EDP due to the late timing of EACD filling. Hence the filling of the EACD can decrease TTI in spite of the increase of aortic EDP because the chamber acts as a compliant blood reservoir in parallel with the aorta for the ejecting LV. This is in contrast to the late deflation data previously presented for the IABP [13]. Late deflation timing of the IABP will increase TTI due to the presence of the balloon in the aorta, which will impede aortic blood flow and increase LV afterload. Later deflation timing during IABP use can cause large left ventricular pressure spikes owing to aortic obstruction by the IAB.

Comment

Mechanical circulatory assistance is indicated in patients with reversible left ventricular failure in whom drug interventions have been unsuccessful or in those awaiting cardiac transplantation in whom pharmacological support is inadequate. Both the LVAD and the total artificial heart have been used for the temporary support of prospective transplant recipients [15] with varying degrees of success. Devices that can be implanted quickly without a complicated procedure could find use in many emergency situations where the IABP is inadequate such as the inability to wean from cardiopulmonary bypass despite support by the IABP or in cases where a weaned patient remains balloon dependent. In addition, they may also be useful in situations where the balloon cannot be inserted due to technical difficulties. The EACD satisfies these requirements because it can be anastomosed to the aorta with a tangential clamp without the need of cardiopulmonary bypass. Its flexible polyurethane construction and small volume facilitate insertion because the device can be folded up, compressed, squeezed, and held out of the way during anastomosis. The extraaortic configuration of this device does not present the same peripheral vascular complications that are associated with an IAB. In addition, the thoracic location of the EACD may allow the patient to ambulate with the IABP console. Finally, the EACD is a simple modification of a new polyurethane artificial ventricle that has been shown to operate for 6 months in calves without any thromboembolic events [16].

Intraaortic balloon pump counterpulsation has established itself as a dominant support intervention for pa-

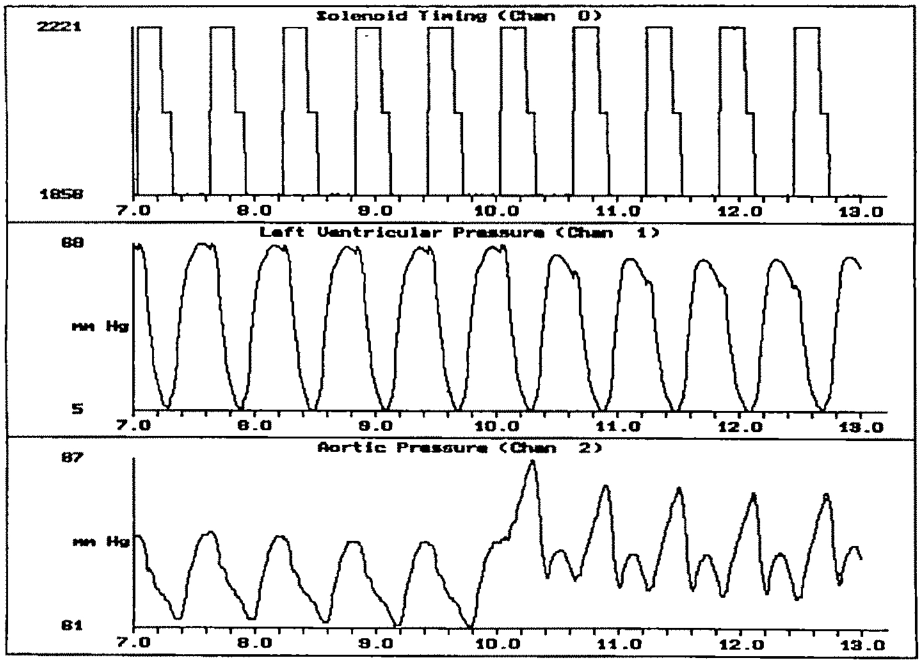

Fig 4. Solenoid timing, aortic pressure, and left ventricular pressure waveforms versus time in seconds for counterpulsation using the extraaortic counterpulsation device when set for late deflation timing conditions. Pressure is in millimeters of mercury. All counterpulsation was performed during cardiac failure.

tients with a variety of cardiac syndromes [2]. It is, however, limited in severe cardiac failure and cardiogenic shock owing to a number of arterial factors. These factors are the proper size relationship between the balloon and aortic diameter, the compliance of the aorta, and the levels of systolic aortic pressure and cardiac output. The IABP operates in a mode in which it displaces a volume of blood inside the aorta at a reasonable distance from the LV. This can lead to degradation of the IABP pressure pulse arising from energy losses due to arterial compliance. Although the IABP can create a vacuum effect during its deflation in the aorta, this effect is again strongly influenced by the aforementioned arterial factors. Since the IABP cannot physically pump blood, all increases in cardiac output that occur during IABP must be directly supplied by the LV ejection. In cardiogenic shock where systemic blood pressure and cardiac output are both low, the IABP cannot operate efficiently due to inadequate volume of arterial blood available for displacement. The IABP can also be timing sensitive, particularly in late deflation where the balloon can obstruct the aorta and actually increase TTI and myocardial oxygen consumption. This problem can have particularly detrimental effects during irregular rhythms.

In contrast, EACD will not be as strongly influenced by arterial factors relative to the IABP because the device is extraaortic. Aortic compliance will affect device filling to a small extent; however, intraaortic pressures and flows will not have a pronounced effect on the EACD. Although EACD is timing dependent, nonoptimal timing will only reduce the benefits obtained relative to unassisted conditions but will never lead to changes in hemodynamics that could potentially harm the patient.

There is one potential shortcoming that can occur during the institution of EACD. Examination of Figure 2 indicates negative flow waves due to device filling in late diastole. These negative flow waveforms indicate that not enough blood is delivered through the LV in severe cardiac failure and that the EACD requires blood volume from the aortic root. If the LV can supply blood, that volume will be taken up by the EACD and LV work will be reduced owing to the siphoning effect of the device. If LV output is low, blood that fills the device will be derived primarily from the arterial circulation and eventually the EACD will fill and eject the same volume of blood into the aorta. This increases the probability of clot formation from stasis in the low-velocity regions of the device owing to a lack of constant "washing" of the EACD with fresh blood. In this regard, both the IABP and the EACD are limited in profound LV failure because both devices derive their blood volume entirely from the LV, although the EACD was clearly more effective for the conditions tested in this study. In these instances, a left ventricular assist device is indicated because it can bypass the LV to obtain a constant fresh blood supply, which will eliminate the possibility of clot formation due to poor washing of the device and maintain adequate systemic perfusion.

This study has demonstrated the effectiveness of the EACD in severe cardiac failure. The extraaortic placement of the device just distal to the aortic valve helps to reduce the dependence of device performance on arterial factors. The EACD is not located directly in the aorta and therefore error in timing adjustments in the deflation phase will only reduce the amount of afterload reduction produced by the device but will never increase afterload greater than unassisted conditions. The EACD can physically deliver and remove a blood volume from the aorta that helps to increase its efficacy of counterpulsation. The results of this study have demonstrated that the EACD has an average beneficial effect on each individual variable of 2 to 10 times that of the IABP. If one estimates the myocardial oxygen supply–consumption ratio using coronary flow as an estimate of oxygen supply and TTI as an estimate of consumption, the EACD increases this ratio by approximately 6 times that of the IABP. This added efficacy of the EACD may prove to be useful in extreme hemodynamic deteriorations, similar to those used in this study.

In summary, the IABP has established itself as an important support modality for patients with cardiac failure. Its ease of insertion and widespread clinical experience have made the IABP an irreplaceable intervention therapy. However, there are instances in which the insertion of the IAB is not technically feasible and situations in which the level of support is inadequate for the severity of cardiac failure. These are the situations in which the implantation of an EACD may be of clinical importance. This study demonstrates the effectiveness of the EACD implanted on the ascending aorta in cases of severe cardiac failure by reducing afterload, augmenting the coronary flow, and consequently, dramatically improving the myocardial oxygen supply–consumption ratio. In addition, the results demonstrated here support the institution of the EACD in situations in which the IABP cannot adequately support the circulation. The use of the EACD deserves further chronic animal studies followed by clinical trials.

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DISCUSSION

DR SHLOMO GABBAY (Newark, NJ): I congratulate Dr Zelano and associates for this interesting confirmation of the previously widely published work on the extraaortic balloon pump.

I hope you are aware that the anatomy of a sheep's aortic arch is very different from that of a human. The sheep has only one large arch vessel that supplies the head and upper limbs. One creates some difficulties by connecting the extraaortic balloon pump to the only arch vessel the animal has: first, you end up killing the animal before termination of the experiment, and second, this arrangement alters the physiology, thus forcing the pump to function in an unnatural environment. Setting up the apparatus in this fashion leaves the investigator with no control of how much blood from the head and upper limb will be affected by the counterpulsation. Why did you not connect the device on the ascending aorta end-to-side?

At this time, I would like to say that the extraaortic balloon pump connected to the ascending aorta is indeed overwhelmingly superior to the standard IABP. My study of the extraaortic balloon pump, published in *ASAIO Transactions* in 1981, clearly showed that bringing counterpulsation closer to the aortic valve can increase coronary flow by as much as 300%. This is striking when one realizes that the IABP only augments coronary flow by

5% to 15%. After the work I published, many investigators reproduced the same results in their laboratories and helped to prove the superior effectiveness of the extraaortic balloon pump. I must confess that I do not understand why the concept is not practiced widely in the clinical setting, and that I was unsuccessful in convincing a commercial outfit to market this device. Hopefully more publications like yours will help to speed the news of this remarkable pump. I have no doubt that in cases where the IABP is not beneficial to the patient, the extraaortic balloon pump will be more effective in helping the heart to recover from temporary ischemia.

DR ROBERT A. GUYTON (Atlanta, GA): I think Dr Kantrowitz and others would object to your calling this a new device, because this is the auxiliary ventricle that he talked about in a counterpulsation mode almost 30 years ago. I agree with the prior discussant that this has been presented before. This is clearly a refinement and a modification of this device using the concepts that we have learned from left ventricular assist devices and associated new technology.

DR ZELANO: It is also a much smaller volume than previous studies. All other studies were done using approximately 70 to 80 mL with some as high as 100 mL. This device is 40 mL; it is effective with a volume as small as 30 mL and can very easily be implanted. The other devices that were made were not practical clinically.

In response to Dr Gabbay's question, the enhancement of the hemodynamics in this study was not as pronounced as in previous studies because we performed our experiments on large animals, approximately 70 to 80 kg with a small device volume of 40 mL. Previous studies used an 80- to 100-mL device on 15- to 20-kg dogs. The great disparity in total blood volume alone more than accounts for the difference we see. Similarly, the differences between the EACD and the IABP were not as pronounced because we used equal displacement volumes for both devices.

Our use of the brachiocephalic artery in sheep was intended to make the operation more technically feasible because of the short ascending aorta in sheep. This configuration also enabled us to measure total aortic flow past the EACD. No flow is shunted to the brachiocephalic because the EACD is implanted there. The increase in sympathetic discharge from the brain is reduced by esmolol as well as ventricular contractility and the entire peripheral vasculature is dilated. We believe that we have produced worst-case conditions for testing the efficacy of counterpulsation, and both devices were alternately tested under identical conditions. Hence this study is representative of what one might obtain clinically.

INVITED COMMENTARY

Dr Zelano and associates have presented additional proof that the EACD or extraaortic balloon counterpulsation pump (EABP) is more efficient than the IABP.

In 1981 we [18] published a thorough comparative study of the EABP and the IABP. Since that time many other groups have continued the research and have published similar studies with practically identical results. It is clear that by bringing the counterpulsation closer to the heart one can increase the coronary flow substantially at the time of diastole and unload the heart at systole in a manner never seen with the IABP. The IABP has several limiting factors that can be overcome by the EABP, and there is no doubt that in many cases when the IABP fails to sustain life a simple valveless device like the EABP can improve the survival rate. As we have seen in our studies the coronary flow can be increased more than 100% using the EABP, compared with 5% to 15% using the IABP.

If the EABP device is so good, why did it not reach clinical use? Indeed, there are several reasons: the device can only be implanted by sternotomy and cannot be introduced through a catheter. For patients in cardiogenic shock, most physicians are reluctant to insert an assist device because it is a relatively invasive procedure, although this fear could be overcome if such a device was widely used and well known.

Second, there is some reservation concerning blood clot formation in a device positioned in the inflow of the large arch vessels. Presently there exist no long-term animal data to preclude this concern, and it is apparent that research must be conducted before any clinical use can be contemplated. If the patient is partially anticoagulated, however, there should be no immediate problem, and many IABPs are inserted through the ascending aorta with no sign of embolic events.

Additionally, the surgical anastomosis between the device and the aorta has not been worked out to a satisfactory level. The width and the length of the cannula are unknown factors. Dr Zelano and associates were not able to eliminate this fear in their recent study because they have cannulated the brachiocephalic artery of the sheep (the only arch vessel supplying the brain and the anterior limbs), which has a relatively large diameter. This vessel is not available in humans. The ascending aorta can be crowded after coronary bypass; therefore, additional research must be performed in this major technical area.

Finally, the industry does not have any "real" interest in sponsoring such a device and government funding was not granted in many instances.

I can only congratulate Dr Zelano and associates for continuing to work on this interesting device. Our group is working toward solving some of the technical/feasibility problems of the EABP. This instrument will, without a doubt, enter the clinical arena proving that patients in cardiogenic shock, who did not respond to the IABP, survived because the EABP was available and used. We must remember that there is nothing wrong in inserting a simple device that all investigators agree can sustain life—especially when the IABP has failed and the EABP can be activated by a widely available balloon pump machine. The patient has nothing to lose!

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Surgical Repair of Aortic Root Aneurysms in 280 Patients

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Bentall's technique for repair of annuloaortic ectasia has been associated with postoperative bleeding and with false aneurysms at the anastomotic site between the coronary orifices and valve-containing graft. To reduce the incidence of these complications, we modified the Bentall procedure, using a simplified technique to implant the graft and to create a fistula between the closed perigraft space and right atrium to control bleeding. A continuous suture of monofilament polypropylene was used to implant the prosthetic valve ring and to anastomose the coronary orifices to the Dacron fabric. In some instances, a brief period of hypothermic circulatory arrest was needed to perform the distal aortic anastomosis. Among 562 patients undergoing operation for aneurysm of the ascending aorta between January 1, 1980, and February 28, 1990, 280 underwent graft replacement with a valve-containing composite conduit. Most (82%) had annuloaortic ectasia. In 267, we performed a classic Bentall procedure with direct anastomosis between the coronary orifices and fabric graft. The remaining 13 patients underwent other procedures for coronary connection. Early mortality was 5.0%. Reoperation for bleeding was needed in 13.2% of patients who underwent operation before we used the right atrial fistula technique and in 4.4% after we began to use the technique ($p = 0.044$). Actuarial survival was 71% at 5 years and 65% at 7 years. For hospital survivors, it was 76% at 5 years and 70% at 7 years. During follow-up, only 9 patients have required reoperation. A false aneurysm at the coronary anastomosis, which was associated with prosthetic valve endocarditis, developed in 1 patient. No permanent fistulas have developed. Thus, by using simplified methods to implant the graft and to control postoperative bleeding, the Bentall technique can be performed successfully with excellent early and late results.

(Ann Thorac Surg 1992;53:38–46)

In 1956, Cooley and associates [1] reported the first use of cardiopulmonary bypass to resect an aneurysm of the ascending aorta. Earlier pioneering efforts to treat ascending aortic aneurysms and aortic arch aneurysms by resection and restoration of flow were limited by both neurologic and cardiac dysfunction [2–4]. Advances since 1956 in the surgical treatment of these pathologic processes have addressed both of these problems. Cooley and DeBakey [5] first suggested that hypothermia was helpful in reducing neurologic complications associated with aneurysm resection. Later, Griepp and colleagues [6] extended this concept by introducing the technique of profound hypothermia and total circulatory arrest. The use of this innovative technique has markedly decreased the operative risk associated with complex reconstructive procedures on the ascending aorta and transverse arch. In 1966, Creech [7] introduced the inclusion technique for repair of aortic aneurysms. In 1964, Wheat and coworkers [8] extended ascending aortic replacement to the aortic annulus, leaving only two small tongues of ascending aorta around the coronary ostia. These techniques were further refined by Edwards and Kerr in 1970 [9]. Miller and associates at Stanford [10] have emphasized this technique in lieu of composite graft replacement with excellent early results. In 1968, the development by Bentall and De Bono [11] of a simple operation for complete replacement of the aortic root further refined the solution for ascending aortic aneurysms and was the first successful attempt at completely excising all diseased ascending aortic tissue. In 1981, Cooley and associates [12] proposed baking the aortic grafts in autologous serum to avoid the profuse bleeding associated with the systemic heparinization required for cardiopulmonary bypass. Later technical modifications by Cabrol and associates [13], including the use of a separate Dacron tube for coronary artery reattachment and the construction of a fistula from the closed perigraft space to the right atrium, have attempted to reduce the incidence of suture line dehiscence and late false aneurysm formation. Kouchoukos and colleagues [14] recommended the abandonment of the inclusion technique in an effort to avoid problems experienced with postoperative hemorrhage and late false aneurysm formation. Other refinements, introduced in 1981 by Livesay and associates [15], included using an open hemiarch repair for treating ascending aortic dissections and aortic arch aneurysms.

Since 1979, we have used a selective approach in the repair of ascending aortic aneurysms and dissections [16].

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Conservative procedures (ie, separate supracoronary tube graft and aortic valve replacement) are used when the aortic annulus and sinuses of Valsalva are only minimally dilated and when the coronary ostia are not elevated away from the annulus. When there is major disease in the aortic root, we prefer total aortic root replacement with a composite graft in an effort to exclude all diseased aortic tissue from the circulation and avoid late reoperation on the aorta and heart to replace the diseased and nonresected aortic valve and sinus portion of the ascending aorta.

We have been impressed with the ease and simplicity of Bentall and De Bono's [11] original operation with direct coronary artery reimplantation and have had excellent early (first 30 days after operation) and late results with a particularly low incidence of technical complications. We present here our experience with aortic root replacements in 280 patients undergoing procedures between 1980 and 1990.

Material and Methods

We retrospectively reviewed case histories of all patients undergoing composite graft replacement of the aortic root from January 1, 1980, to February 28, 1990. Of 562 patients undergoing operation for ascending aortic disease during this period, 280 patients underwent composite graft replacement of the ascending aorta. The remaining 282 patients underwent various procedures to repair ascending aortic and aortic arch aneurysms and are excluded from this study.

For the purpose of this study, a neurologic complication was defined as any lateralizing deficit or any diffuse neurologic change or deficit that was present postoperatively but not preoperatively. Early mortality included all patients who died before they could be discharged from the hospital or within 30 days of their original operation. Valve thrombosis was defined as the presence of a thrombus on the aortic valve at the time of reoperation. Embolic events were attributed to the aortic valve prosthesis if definite evidence showing valve thrombus was found or if no other cause could be found for a sudden neurologic event occurring late postoperatively.

We examined the hospital and office charts of the 280 patients for the following factors: age, sex, preoperative New York Heart Association (NYHA) class, type of aortic valve disease (aortic stenosis or aortic insufficiency), cause of their disease, previous cardiac operations, the need for emergency operation, the use of circulatory arrest and its duration, the method of coronary artery reattachment, the use of a fistula from the closed perigraft space to the right atrium, use of the inclusion technique, other concomitant operative procedures, type of prosthetic valve used, date of operation, cross-clamp time, duration of cardiopulmonary bypass, the need for return to the operating room for control of bleeding, and major early postoperative complications including heart block, neurologic deficits, early prosthetic valve endocarditis, wound infection, acute renal failure, and early (30-day hospital) mortality and its cause. Late follow-up was conducted by phone interview or questionnaire with the patient and referring physician.

For the period after the first 30 days, we recorded the date of follow-up or death, cause of death, date of reoperation on the heart or ascending aorta, NYHA class, presence of pseudoaneurysm, persistent perigraft to right atrial fistula, paravalvular leak, thromboembolic events, late prosthetic valve endocarditis, other operations performed on the remaining aorta, and the presence of a late dissection in the remaining aorta.

Statistical Methods

The actuarial life-table method [17] was used to estimate survival and event-free rates, and comparisons of actuarial curves were done using the Cox-Mantel test [18]. Deaths from all causes were included in the survival analyses. A *p* value of 0.05 was considered statistically significant.

Operative Technique

In 267 of the 280 cases (95.4%) of aortic root replacement, we (ourselves and others at the Texas Heart Institute) used the Bentall operation with direct coronary artery reimplantation. Cardiopulmonary bypass is initiated with the arterial cannula in the ascending aorta, the transverse arch, or the femoral artery, depending upon the extent of the aneurysm and the presence or absence of dissection. Venous return is by bicaval cannulation, preserving the right atrial appendage for later use. Recently, we have tended to use the femoral artery almost exclusively for return of oxygenated blood. Its use is mandatory in aortic dissections and arch aneurysms but helpful in all cases because it allows full access to the ascending aorta, the transverse arch, and the brachiocephalic vessels.

Cardiopulmonary bypass is instituted with moderate systemic hypothermia (30°C). When it is necessary to repair a type A dissection or to repair a transverse arch aneurysm, we use profound hypothermia and total circulatory arrest at systemic temperatures of 20° to 22°C along with an open technique for hemiarch repair as originally described by Livesay and associates [15]. After the institution of cardiopulmonary bypass, the ascending aorta is cross-clamped and the heart is arrested with cold hyperkalemic crystalloid cardioplegia. A sump is placed in the right superior pulmonary vein. A longitudinal aortotomy is made and extended into the noncoronary sinus of Valsalva, well away from the right coronary ostium. The valve is excised and a valve conduit, previously baked in autologous serum, is sewn to the annulus with a continuous 2-0 polypropylene suture (Fig 1). Two "buttons" of graft are excised with a hand-held cautery, and the left and right coronary ostia are sewn directly to these holes with a running 4-0 polypropylene suture (Fig 2); the sutures are placed in the aorta around the coronary ostia, not *in* them. This important technical maneuver may prevent late stenosis, as well as late formation of false aneurysm. Particular attention is directed to making a watertight anastomosis. If the aneurysm is limited to the ascending aorta and there is no associated dissection, the graft is tailored and the distal anastomosis completed with

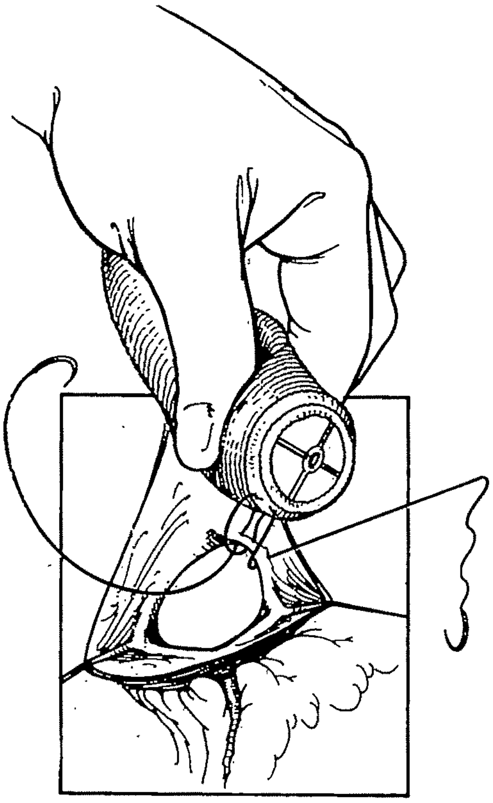

Fig 1. After removal of the aortic valve leaflets, the proximal anastomosis of the valve sewing ring is performed with a continuous 2-0 polypropylene suture.

the aortic cross-clamp in place by using the inclusion technique originally described by Creech [7]. Rewarming is begun while the distal anastomosis is being sewn. The cross-clamp is removed, and the air in the ascending aorta and heart is removed. Cooley caval clamps are placed around the caval cannulas and a fistula is constructed from the perigraft space to the right atrium as described by Cabrol and associates [19] by sewing the proximal apex of the aortotomy to a 2-cm slit in the medial aspect of the right atrial appendage (Fig 3). The remaining aorta is snugly wrapped around the graft. The patient is weaned from cardiopulmonary bypass, and the cannulas are removed.

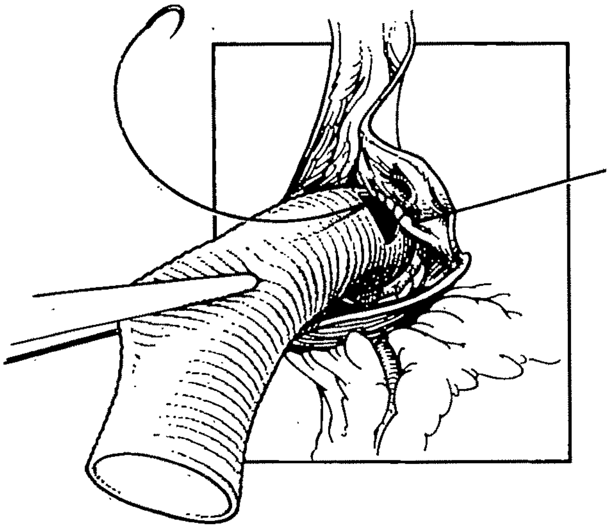

Fig 2. Coronary orifices are anastomosed to the woven Dacron graft with a continuous 4-0 polypropylene suture.

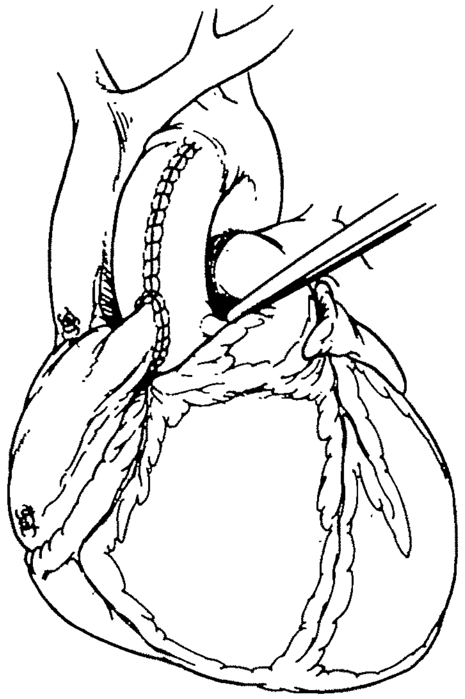

Fig 3. A fistula is created between the perigraft space and right atrium.

In cases in which there is an associated type A dissection of the ascending aorta or aneurysmal involvement of the aortic arch, the operation is modified. During completion of the proximal anastomosis and reimplantation of the left coronary ostium, the patient's temperature is lowered to 20° to 22°C. The pump is turned off, the lines are clamped, and circulatory arrest is initiated. The patient is placed in a steep Trendelenburg position, the aortic cross-clamp is removed, and the distal anastomosis is completed. In a case of aneurysm of the transverse aortic arch, a long tongue of graft is cut to allow tangential replacement of the aortic arch along its lesser curvature (Fig 4). In a dissection, the aorta is completely transected distal to the intimal tear, and the distal anastomosis is sewn end-to-end in an effort to completely obliterate the false lumen, using a felt strip to reinforce the anastomosis. Hemostasis of the anastomosis can be improved by using a nerve hook. The right coronary artery is reimplanted while the patient is rewarmed and the operation is completed as above except in cases in which the aorta has been completely divided distally. In these patients (with dissection), the inclusion technique with a Cabrol fistula cannot be used and the remaining aorta is loosely approximated over the repair. The distal anastomosis in these operations is usually wrapped with a 12-mm Dacron tube graft.

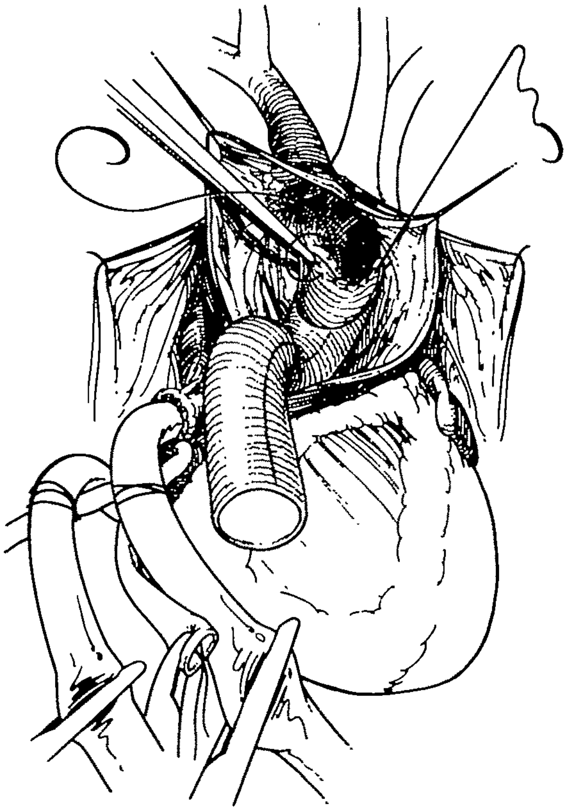

Fig 4. When the aneurysm involves the transverse aortic arch, an "open" anastomosis is performed during the temporary hypothermic circulatory arrest.

Patients and Treatment

The average age of the 68 female (24%) and 212 male patients (76%) was 47.1 years (range, 6 to 80 years). Preoperatively, 4 (1.4%) patients were in NYHA functional class I, 61 (21.8%) in class II, 171 (61.1%) in class III, and 44 (15.7%) in class IV.

Indications for operation were the presence of an aneurysm or aortic dissection associated with serious aortic insufficiency in 267 (95.4%), combined severe aortic stenosis and aortic insufficiency in 12 (4.3%), and isolated severe aortic stenosis in 1 (0.3%).

Two hundred fifty-eight (92%) underwent elective operation, and 22 (8%) had emergency procedures primarily for acute aortic dissection. There were no luetic ascending aortic aneurysms.

Two hundred fifty-one (89.6%) patients had primary operations, 24 (8.6%) secondary operations, 4 (1.4%) tertiary operations, and 1 patient underwent a fourth operation on the aortic root. Of the 280 patients who had operation, 267 (95.4%) underwent the Bentall procedure with direct coronary ostia reimplantation. Of the remaining 13 (4.6%), 3 underwent a standard Cabrol procedure and 9, a modified Cabrol procedure. In 1, the coronary orifices were oversewn and coronary artery bypass was performed with the use of saphenous veins.

Eighty-three patients (29.6%) underwent concomitant procedures: isolated coronary artery bypass, 32; mitral valve repair or replacement, 5; ascending-descending aorta bypass, 3 (to correct persistent or recurrent coarctation of the thoracic aorta); coronary artery bypass and mitral valve repair or replacement, 2; atrial septal defect repair, 1; innominate artery bypass, 1; and wedge resection of a solitary pulmonary nodule, 1. In 38 patients (13.6%), the graft was extended to include repair of an aneurysm of the transverse arch. A Björk-Shiley composite graft prosthesis was used in 153 (54.6%), and in 127 (45.4%), a St. Jude composite graft was used. Now we use the St. Jude composite graft prosthesis exclusively. Cross-clamp times ranged from 24 to 215 minutes (mean, 50 minutes). The duration of cardiopulmonary bypass ranged from 32 minutes to 283 minutes (average, 70 minutes). Circulatory arrest was used in 65 patients (23.2%) (duration, 4 to 21 minutes; mean, 10.3 minutes). The distal anastomosis was in the distal ascending aorta in 86.4% of the patients and the proximal, mid, or distal transverse arch in 13.6%. The inclusion technique was used in 192 (68.6%) patients, and in 68 of these (35.4%) a perigraft space to the right atrial fistula was constructed.

Results

Early Mortality

Our early mortality of 5% compares favorably with that of other studies [14, 16, 19–22]. Reports of mortality range from 4.7% to 9.0%. Causes of death in our patients included coagulopathy or hemorrhage (intraoperative) in 4, low cardiac output in 3, and ventricular fibrillation in 2. Five others died of 5 different causes: myocardial infarction (8 days postoperatively), delayed tamponade (4 days postoperatively), brain death, respiratory arrest (multisystem failure), or cardiac arrest (complete heart block).

Factors related to early mortality shown to be statistically significant included classification into NYHA class III or IV ($p = 0.006$) and cross-clamp times greater than 60 minutes ($p = 0.004$). Prolonged cardiopulmonary bypass was associated with an increased risk of early death ($p = 0.002$). Postoperative complications associated with an increased risk of early death included hemorrhage ($p = 0.032$), neurologic deficit ($p = 0.041$), and heart block ($p = 0.016$). In addition, emergency operation was associated with mortality seven times as great as elective operation ($p < 0.000$). Likewise, patients who required concomitant coronary artery revascularization were more likely to die during the first 30 days (17.6%) than those whose coronary circulation was normal (3.3%) ($p = 0.001$). Patients with infected valves had a 20% mortality, but those whose valves were not infected had a mortality of 4.7% ($p = 0.120$). Those with either an isolated type A dissection or a dissection superimposed on underlying annuloaortic ectasia were also more likely to die within 30 days postoperatively (mortality, 8.3%) than were those without a dissection (mortality, 4.1%), but this difference was not statistically significant ($p = 0.105$). Mortality associated with pure, isolated annuloaortic ectasia was 3.6% ($p = 0.109$) (Table 1). Although aortic stenosis was associated with an increased mortality compared with isolated aortic insufficiency (8.3% versus 4.9%), the increase was not

Table 1. Diagnosis and Early Mortality

Diagnosis	N	Deaths	Mortality (%)
Annuloaortic ectasia	194	7	3.6
With dissection	32	0	0
With endocarditis	3	0	0
Isolated dissection	28	5	17.9
Isolated subacute bacterial endocarditis	2	1	50.0
Atherosclerosis	11	1	9.1
Miscellaneous aortic diseases	6	0	0
Rheumatic valvulitis	4	0	0
Total	280	14	5.0

statistically significant ($p = 0.85$). Finally, early mortality was also higher in patients who underwent a repair other than a classic Bentall operation than it was in those who underwent a Bentall procedure (15.4% versus 4.5%; $p = 0.079$); however, this difference was not significant.

Factors unrelated to early mortality included old age (>70 years), being female, and the type of valve used. Other factors that did not appear to increase the risk of early death included concomitant procedures (including concomitant arch repair), repeat operative procedures on the ascending aorta, and use of hypothermia and total circulatory arrest.

Postoperative Hemorrhage

Return to the operating room for control of hemorrhage was required in 31 patients (11.1%) and was associated with an increased risk of early death, those returning to the operating room having a 12.9% mortality compared with 4% for those not requiring a return ($p = 0.032$) (Table 2). Two patients who required late reoperation for repair of a pseudoaneurysm at the distal aortic suture line were taken back to the operating room early for postoperative hemorrhage. This may represent an early manifestation of pseudoaneurysm formation. In neither of these patients was the inclusion technique or the perigraft to right atrial fistula used.

Postoperative Neurologic Deficit

Neurologic deficits were detected in 11 (3.9%) patients postoperatively, and in 5 (1.8%), these were permanent. Neurologic complications did occur more frequently in patients in whom profound hypothermia and total circulatory arrest were used (10.8% compared with 1.9%; $p = 0.001$) and in patients with dissection (6.7% compared with 3.2%; $p = 0.218$). Emergency operation was associated with a higher rate of neurologic complications (13.6% compared with 3.1%; $p = 0.015$). Early mortality was significantly higher in patients who sustained a perioperative neurologic insult (18.2% compared with 4.5%; $p = 0.041$). Other postoperative complications are listed in Table 3.

Table 2. Factors Associated With Postoperative Hemorrhage Requiring Early Return to the Operating Room

Factor	No. Requiring Return/N	Percent	p Value
Repeat operations	5/29	17.2	0.08
Primary repairs	26/251	10.4	
Dissection	9/60	15.0	0.053
All other diagnoses	20/215	9.3	
Endocarditis	2/5	40.0	
Non-Bentall repair	3/13	23.0	0.69
Bentall repair	28/267	10.5	
Profound hypothermia and total circulatory arrest	11/65	17.0	0.086
Moderate systemic hypothermia	20/215	9.3	
Inclusion technique	17/192	8.3	0.01
No inclusion technique	14/88	17.0	
Cabrol fistula	3/68	4.4	0.04
No fistula	28/212	13.2	

Long-Term Follow-up

Of all hospital survivors, 241 (90.6%) were available for follow-up in intervals ranging from 1 month to 123 months (mean, 46 months). A number of foreign nationals were not available for follow-up and are excluded from long-term studies. Follow-up consisted of a questionnaire directed to patients and their physicians. Actuarial survival of all those patients surviving initial hospitalization was 95% at 1 year, 76% at 5 years, and 70% at 7 years (Fig 5). Forty-two patients died after surviving an initial 30-day postoperative period. Ten deaths were related to late aortic dissection, rupture, or reoperation. Five deaths were attributed to congestive heart failure, another 5 to

Table 3. Postoperative Complications and Their Relation to Early Mortality

Complication	No. With Complication	Percent	p Value
Hemorrhage	31	11.1	0.032
Neurologic deficit	11	3.9	0.001
Permanent	5	1.8	
Complete heart block	9	3.2	0.016
Permanent pacemaker implantation	7	2.5	
Wound infection	6	2.1	0.57
Renal dysfunction	6	2.1	0.19
Permanent renal failure	1	0.4	
Early prosthetic valve endocarditis[a]	2	0.7	0.69

[a] Both of these patients died of endocarditis within 3 months of discharge from the hospital.

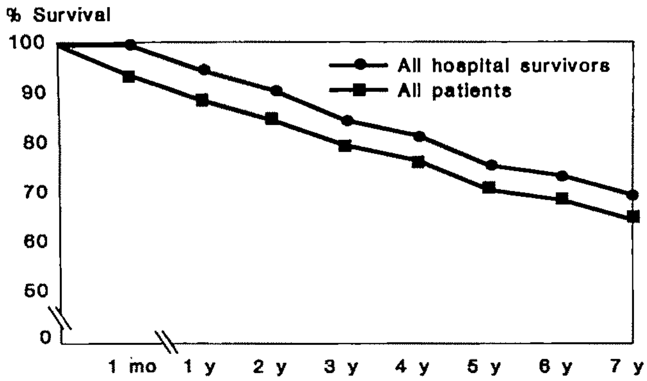

Fig 5. Overall actuarial survival.

myocardial infarction, 2 to arrhythmia, and 1 to prosthetic aortic valve thrombosis. Various other causes included cancer (6), stroke (3), renal failure (1), and sepsis (1). The remaining 8 patients died of unknown causes.

Late survival was adversely affected by severe preoperative cardiac dysfunction indicated by the patients' classification into preoperative NYHA class IV. Actuarial survival in this group was 72% at 1 year and 56% at 5 and 7 years (Fig 6). Myocardial infarction and congestive heart failure, together with other cardiac problems, accounted for more than one-third of all late deaths. The presence of a dissection was also associated with a higher risk of death in this period (Fig 7). Disease of the remaining aorta was a significant cause of death in the population, reflecting the experience of other authors. Aortic disease accounted for ten late deaths (including two operative deaths; 4.8%), or 24.4% of all late deaths. Late reoperation on the remaining aorta was required in 12 patients and 2 of these died. In summary, 20 patients (9.5% of all patients followed up long-term) either died of or underwent reoperation for persistent or recurrent disease in the remaining aorta after aortic root replacement.

During long-term follow-up, there were 13 conduit or aortic valve-related complications. Six patients had thromboembolic complications associated with their aortic valve: 2 of those patients with thrombosed aortic valves required reoperation; 1 of them died. Four patients sustained embolic strokes and did not require reoperation.

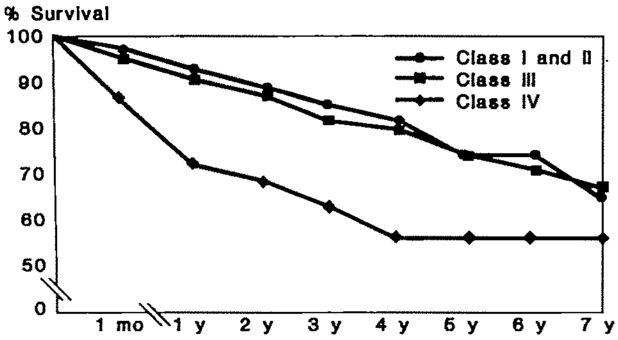

Fig 6. Comparison of actuarial survival according to preoperative New York Heart Association functional class assessment.

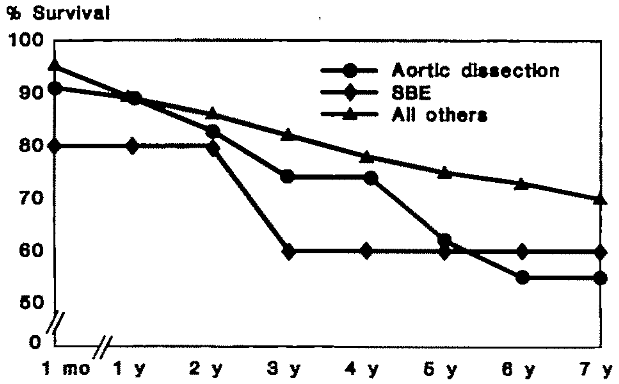

Fig 7. Comparison of actuarial survival according to cause of aneurysm. (SBE = subacute bacterial endocarditis.)

Three patients had late prosthetic valve endocarditis. Both of these undergoing reoperation died, but the third patient was treated medically and survived. Two pseudoaneurysms were reported at the distal aortic anastomosis. In both patients, reoperation was required for control of hemorrhage. One pseudoaneurysm of a coronary anastomosis occurred at the site of reimplantation of the left coronary ostium. At reoperation, the pseudoaneurysm was infected, and we believed that this aneurysm was the result of prosthetic valve endocarditis and did not reflect a technical complication per se. Two patients had late paravalvular leaks. In both, the composite graft was constructed at the time of operation, and a commercially prepared conduit was not used. Paravalvular leak has not occurred in any patient in whom we used a commercially prepared composite graft. We have seen no evidence at follow-up of persistent fistulas between the perigraft space and the right atrium. In 1 patient with persistent left ventricular failure, a cardiac transplantation was performed 6 months postoperatively, and he remains alive and well. Late survival was not affected by the type of valve used. In summary, reoperation on the heart or ascending aorta has been required in 9 patients, and 3 (33.3%) died.

Postoperative cardiac function was significantly improved, as evidenced by a statistically significant change in the proportion of patients in NYHA classes I or II ($p <$ 0.000) (Fig 8). Persistent cardiac failure, however, remains a significant cause of premature late death as evidenced by five late deaths related to congestive heart failure and the need for cardiac transplantation in 1 patient with persistent congestive heart failure.

Comment

Since Cooley and DeBakey's original reports [1–5] of repair of ascending aortic aneurysms, mortality and major complications for these operations have been declining. Various technical approaches are available for managing combined ascending aorta and aortic valve pathology, and each has its supporters [10, 13, 14, 16, 20]. Since 1979, at the Texas Heart Institute we have selectively employed various techniques for the repair of ascending aorta and

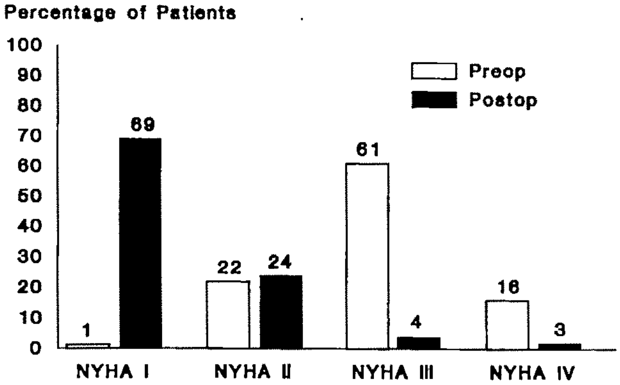

Fig 8. Comparison of preoperative and postoperative New York Heart Association (NYHA) functional class in patients who survived operation.

aortic arch aneurysms [16]. When we find associated major disease of the sinuses of Valsalva and the aortic annulus, we prefer composite graft replacement for aortic aneurysm repair. We follow the technique described by Bentall and De Bono [11] in 1968 with direct coronary artery reimplantation using the inclusion technique when possible. Recently, we have added the routine construction of a perigraft to right atrial fistula, a maneuver described by Cabrol and associates [19]. This operation can be done with short ischemic and short cardiopulmonary bypass times with the expectation of excellent early and late results.

The use of a conventional or conservative operation as described by Wheat and co-workers [8] is appropriate for patients who do not have disease of the sinus portion of the aortic root, which would necessitate composite graft replacement. Indeed, this procedure was used in many of the 282 patients having ascending aortic aneurysm repair during this 10-year period who did not have composite graft replacement of the aortic root.

Complete aortic root replacement with a composite graft has a number of advantages over the conventional operation when there is disease involving the aortic annulus and sinuses of Valsalva. First, all diseased aortic tissue is eliminated from the aortic root. Second, the operation is conceptually simple and easy to perform. Third, by using the inclusion technique along with construction of a fistula from the perigraft space to the right atrium, bleeding complications are minimized, as is the incidence of late false aneurysm formation at the coronary artery reimplantation sites or compression of the neoaorta by hematoma formation in the supravalvular position. This represents a marked change from our previous views [16]. Construction of a fistula, however, is no substitute for accurate hemostatic suturing. Hemostasis is also enhanced by baking the graft in autologous serum [12]. Complete hemostasis is mandatory, as our data indicate that return to the operating room for bleeding is associated with a statistically significant increased risk of hospital death. Two of the 3 patients undergoing late reoperation for aneurysm formation had early reoperation for hemorrhage, perhaps an early manifestation of pseudoaneurysm formation.

When possible, we prefer the classic Bentall approach to that of a Cabrol modification with the interposition of a synthetic tube graft between coronary ostia. Despite this, the results of many groups employing this technique (particularly those of Cabrol himself and Crawford) are exemplary and comparable with our experience [13, 22]. We prefer to avoid the placement of a prosthetic tube graft into the coronary circulation. We do, however, occasionally use the Cabrol operation or a modification thereof in a situation where direct reimplantation is difficult (ie, where the coronary ostia are quite low, less than 1.5 cm above the annulus). Factors that were correlated with early mortality in general are not associated with the type of repair used. Early mortality is, instead, related primarily to the presence of severe left ventricular dysfunction (NYHA class III or IV), the need for emergency operation, the presence of coronary artery disease requiring the addition of coronary artery bypass grafting, and severe postoperative hemorrhage requiring early reoperation. This, in general, is in agreement with several other recent reports [13, 14, 16, 22]. We agree with Galloway and colleagues [20] that there is a decreased incidence of early return to the operating room for hemorrhage when the inclusion technique and the construction of a perigraft to right atrial fistula are used. This contrasts with data from other institutions that associated the use of the inclusion technique not only with a high rate of early reoperation for bleeding but also with a higher incidence of late false aneurysm formation at the suture line [14, 22–26]. We have observed a very low incidence of false aneurysm formation at the coronary artery reimplantation sites and an especially low incidence of bleeding complications in those patients in whom the inclusion technique was used along with the construction of a fistula from the perigraft space to the right atrium. The inclusion technique should be used selectively, however. In repairing a type A dissection, we advocate complete transection of the aorta distally with the use of total circulatory arrest and an open hemiarch repair [15]. Transection of the aorta at its distal site precludes the use of an inclusion technique and also the use of a fistula. In these instances, the distal anastomosis is usually supported with a 12-mm Dacron tube graft wrapped around the anastomosis.

Early and late complications related to the operation are few, and late reoperation for a technical problem is unusual. Late reoperation for pseudoaneurysm formation was necessary in only 3 patients and was not associated with the use of the inclusion technique or with the use of the perigraft to right atrial fistula. Although there is a report of persistence of the perigraft to right atrial fistula in the literature, we have not seen this complication [27]. Indeed, most problems are related more to the use of a prosthetic aortic valve than to replacement of the ascending aorta or the technique for coronary artery reimplantation. Again, we favor a selective approach based on the findings at operation. Late survival is profoundly influenced by remaining aortic disease. Late reoperation on the remaining aorta or death from complications related to residual aortic disease is common and has been emphasized by others [13, 14, 19, 23]. This underscores the importance of attempting to obliterate the false lumen in operations for type A dissections and has led us to routinely transect the aorta distally in these patients, using the technique of profound hypothermia and total circulatory arrest. With the open hemiarch repair distal to the area of aortic cross-clamp and the intimal tear, the inner and outer layer can be accurately reapproximated to establish flow into the true lumen. Other surgeons outside of the United States [13, 19] have used a biologic glue to aid in the repair of dissections, with impressive results. Finally, patients with aortic root aneurysms must be followed up closely, not only for problems related to their operation but for the detection of surgical disease in the remaining aorta. Late reoperation on the remaining aorta will become increasingly common as these patients are followed up for extended periods.

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DISCUSSION

DR NICHOLAS T. KOUCHOUKOS (St. Louis, MO): More than 20 years' experience with composite graft replacement of the ascending aorta and aortic valve, described by Bentall and DeBono in 1968, has established this procedure as the treatment of choice for annuloaortic ectasia and for other disorders of the aortic sinuses and ascending aorta, most commonly aortic dissection, that are associated with aortic regurgitation. On this there is almost universal agreement.

There is disagreement, however, about the optimal technique for insertion of the composite graft. Bentall used what can be termed the inclusion-wrap technique, also advocated by Dr Lewis and his associates, to reduce the frequency of serious bleeding problems which were commonly encountered in the early years that this procedure and other operations on the ascending aorta and aortic valve were performed.

Several important modifications in technique have been introduced that I believe obviate the need for the inclusion-wrap technique. These include preclotting of the grafts with plasma or albumin, which eliminates interstitial bleeding; interposition of venous or synthetic grafts between the coronary ostia and the tube graft, which reduces tension on the coronary arterial suture lines; and use of fibrin glue or other adhesives, which seals bleeding points at these suture lines.

In contrast to Lewis and associates, we observed a significantly lower incidence (2%) of reoperations for bleeding among patients in whom the aneurysms were excised, the open technique, than among the patients in whom the inclusion technique was employed, where the incidence of bleeding was 13%. We have not found it necessary to create a fistula from the aortic wall to the right atrium in any patient. It may, on rare occasion, be a useful adjunct when bleeding cannot be controlled by conventional measures.

In a follow-up of 105 patients in whom the inclusion-wrap technique was used, we found a 9% incidence of pseudoaneurysms at the coronary or distal aortic suture lines. Seven of these 9 patients required reoperation, and 1 patient required this procedure 11 years after the initial procedure.

In contrast, looking at an actuarial analysis, none of the patients in the open group has required reoperation for this complication. One pseudoaneurysm did develop in the open group, but this was related to a spontaneous tear that occurred in the Dacron portion of the composite graft.

We have found a significant difference in freedom from reoperation on the ascending aorta for any cause in favor of the open technique.

I have several questions for Dr Lewis. Are you confident that the reduced reoperation rate for bleeding is due to the right atrial fistula and not to other refinements or alterations in technique, and do you recommend that it be used routinely? You stated in the manuscript that there have been no persistent fistulas between the perigraft space and the right atrium. What techniques did you employ to document closure of the fistula? Closure of the fistulas in all cases has not been observed by others who have used this modification. Persistent patency may indicate the presence of a pseudoaneurysm or a leak at one of the suture lines. You also indicate in the manuscript that a number of foreign nationals were not available for follow-up and were excluded from the long-term analyses. Can you tell us what percent of the total group this represents and what effect this might have on the incidence of late complications, particularly pseudoaneurysms? It is clear from other studies that when angiography, computed tomography, or magnetic resonance imaging is used, the incidence of pseudoaneurysms is higher than that observed by clinical evaluation only.

This is an important paper, which confirms the safety with which the composite graft technique can be performed and also documents the adverse effect of recurrent or persistent aneurysm formation in the residual aorta on long-term outcome.

DR LARS SVENSSON (Houston, TX): I rise to congratulate the authors of this paper on annuloaortic ectasia, a term that was originally coined by Dr Cooley. Two years ago Dr Crawford presented our series of 717 patients, with the subgroup of annuloaortic ectasia having the lowest operative mortality rate. We now have a series of 1,049 patients with ascending aorta and arch replacements and continue to have a 96% survival rate for the subgroup of patients with annuloaortic ectasia [1]. However, we have abandoned the technique of Bentall and we have only operated on 1 patient in the last 2 years using that technique.

In our recent analysis, especially in those patients with aortic dissection and in 151 patients with Marfan's syndrome, we have observed that there is a high incidence of reoperation in patients who have had the Bentall type of repair. We noted that at the proximal suture line, especially if a continuous suture was used, the annulus tore and the valve became displaced. We also noted that pseudoaneurysms developed at the reimplantation site of the coronary artery ostia to the composite graft. Subsequently, in an analysis of our patients who have had the Cabrol type of repair, or implantation using the coronary ostial button technique, we have had no reoperations for pseudoaneurysms. For these operations we also used the open technique described by Dr Kouchoukos.

I therefore have a question for Dr Lewis. Although we have noted that, with the Cabrol technique, the right coronary artery graft can occlude unless it is carefully lined up in a direct position toward the right coronary artery, have you modified your technique in patients with aortic dissection or with Marfan's syndrome?

DR LEWIS: I thank Dr Kouchoukos and Dr Svensson for their comments. In regard to the question on the use of the right atrial fistula, in patients in whom the aorta is not transected and in whom an inclusion technique is possible, we routinely employ the fistula. We do not, however, regard the fistula as a panacea for bleeding after the repair and emphasize hemostatic control at all suture lines before its construction.

The use of the continuous suture technique is important, specifically when you are reimplanting the coronary ostia (not entering the coronary artery itself). Then, the aortic wall allows a good purchase on the aorta and fewer problems with bleeding. The fistula, we believe, decompresses the area of the perigraft space and prevents buildup of blood and perhaps pressure that might cause either supravalvular stenosis or a tearing effect on the coronary ostia reimplantation sites. We have not specifically looked for recurrence of the fistula with any particular method.

Long-term follow-up of patients, as you know, is essential. All receive anticoagulation for which they see their physicians routinely. We recommend chest roentgenograms as part of the routine follow-up. In patients with the clinical stigmata of Marfan's syndrome, aortic dissection, or documented aneurysmal disease of the remaining aorta, we also recommend that either contrast-enhanced computed tomography or magnetic resonance imaging be employed at least biannually. A minority of patients in these groups will be well served by staged reoperation. Most of our patients were available for follow-up: 90% had complete follow-up, and 10% were lost to follow-up. Approximately 90% of the latter group were from outside of the United States.

For the most part, we have avoided the use of the Cabrol modification because we question the long-term durability of this Dacron graft. In general, our approach is modified only in the situation wherein primary dissection is present and the coronary ostia are not elevated away from the annulus. The ostia, however, can be reimplanted at a level lower than we previously thought possible.

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Retrograde Cerebral Perfusion Through a Superior Vena Caval Cannula Protects the Brain

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Retrograde cerebral perfusion through a superior vena caval cannula is a new technique for protecting the brain during aortic arch operations. In mongrel dogs (n = 10; 13 to 15 kg) we have performed retrograde cerebral perfusion (300 mL/min) by infusing blood through a superior vena caval cannula with aortic and inferior vena caval drainage. We have measured the cerebral tissue blood flow, oxygen consumption, and carbon dioxide exudation during retrograde cerebral perfusion at normothermia (NT, 37°C) and hypothermia (HT, 20°C) and have compared these values with values obtained in dogs during cardiopulmonary bypass (1,200 mL/min). Cerebral tissue blood flow was measured by the hydrogen clearance method. During retrograde cerebral perfusion about 20% of the superior vena caval perfusate was returned through the aorta and the rest drained from the inferior vena cava. Cerebral vascular resistance during retrograde cerebral perfusion was lower than that during cardiopulmonary bypass (NT, 63.8 ± 52.5 versus 126.9 ± 58.4; HT, 28.4 ± 32.8 versus 69.5 ± 28.7 × 10^3 dynes · s · cm^{-5}). Retrograde cerebral perfusion provided half the cerebral tissue blood flow of cardiopulmonary bypass (NT, 14.7 ± 6.4 versus 34.3 ± 7.8; HT, 17.6 ± 5.6 versus 37.2 ± 10.6 mL/min). Retrograde cerebral perfusion also provided a third of the oxygen (NT, 4.4 ± 2.1 versus 12.3 ± 7.1; HT, 1.4 ± 0.8 versus 4.2 ± 1.3 mL/min) and discharged 20% of the carbon dioxide (NT, 0.24 ± 0.08 versus 1.19 ± 0.58; HT, 0.15 ± 0.06 versus 0.51 ± 0.17 mmol/min) when compared with cardiopulmonary bypass. Retrograde cerebral perfusion may reduce ischemic damage during interruption of cerebral blood flow.

(Ann Thorac Surg 1992;53:47–53)

During aortic arch operations, protection of the brain while cerebral blood flow is interrupted is important. Deep hypothermic circulatory arrest or isolated cerebral perfusion has been commonly used for brain protection during aortic arch operations [1–5]. However, circulatory arrest can be tolerated for only a limited period of time even with deep hypothermia. Isolated cerebral perfusion requires complicated and potentially hazardous cannulation techniques. Retrograde cerebral perfusion (RCP) through a superior vena caval cannula is a new and simple technique for brain protection [6, 7]. Since January 1990 we have applied RCP in 15 patients undergoing aortic arch operations. All except 2 patients recovered consciousness clearly on the first postoperative day. We have undertaken an experimental study to evaluate cerebral tissue blood flow, oxygen consumption, and carbon dioxide exudation in the mongrel dog with cardiopulmonary bypass (CPB) and RCP at both normothermia and hypothermia.

Material and Methods

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by National Institutes of Health (NIH publication No. 85-23, revised 1985).

Preparation of Animals and Cardiopulmonary Bypass Methods

Ten mongrel dogs weighing 13 to 15 kg were used for this study. Anesthesia was induced with ketamine hydrochloride, 10 mg/kg intramuscularly, and thiopental sodium, 5 mg/kg intravenously. After endotracheal intubation, the animal was ventilated mechanically with 100% oxygen. The ventilator rate and tidal volume were adjusted to maintain the arterial carbon dioxide tension around 35 mm Hg. Anesthesia was maintained with intravenous ketamine hydrochloride, 2 mg · kg^{-1} · h^{-1}.

Catheters were placed in the right carotid artery, the right external jugular vein, and the right femoral vein for withdrawal of blood samples and measurement of blood pressure. The cerebral tissue blood flow was measured using the hydrogen clearance method with RBF-2 (Biomedical Science Inc, Tokyo, Japan) [8, 9]. A hydrogen

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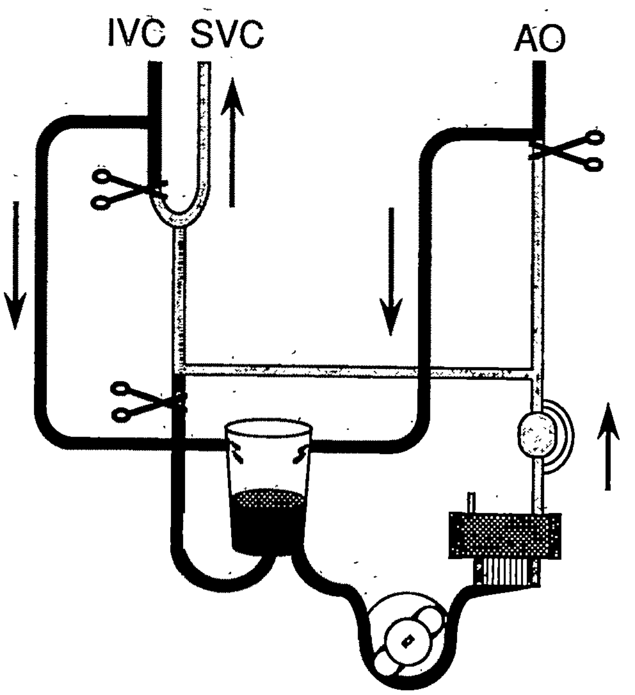

Fig 1. Perfusion and drainage system in retrograde cerebral perfusion through a superior vena caval cannula. Returned blood (black) *from the inferior vena cava* (IVC) *and aorta* (AO) *was drained into a cardiotomy reservoir and was pumped through a oxygenator into the superior vena cava* (SVC) (light gray).

electrode was inserted into the inner cerebral cortex of the midcentral parietal lobe through a burr hole in the skull. Cerebral tissue blood flow was calculated, subtracting that at total circulatory arrest.

A thoracotomy was made through the right fourth intercostal space. Heparin, 300 U/kg, was given intravenously. The ascending aorta and the right atrium were cannulated with two separate venous cannulas, and vena caval tapes were applied. Cardiopulmonary bypass was established at a flow rate of 1,200 mL/min with occlusion of the azygos vein. To switch to RCP, a cross-clamp was applied to the ascending aorta and the heart was arrested with intermittent cold crystalloid cardioplegia. After a brief period of circulatory arrest, RCP was established with blood perfusion through the superior vena caval cannula and aortic and inferior vena caval drainage (Fig 1). The pump circuit consisted of a Capiox 0.8-m^2 oxygenator with a cardiotomy reservoir (BPC-350; Aika, Tokyo, Japan) primed with electrolyte solution and 500 mL of blood from another dog. No interventions were made to control blood pressure during this study.

Experimental Protocol

Cardiopulmonary bypass was begun with a flow rate of 1,200 mL/min (control CPB) at normothermia (37°C). After 10 minutes perfusion was switched to RCP with flows of 300 mL/min (RCP 300), 200 mL/min (RCP 200), and 100 mL/min (RCP 100) during three consecutive 10-minute experimental periods. Cardiopulmonary bypass was then reestablished with a flow rate of 1,200 mL/min. The animal was cooled to a nasopharyngeal temperature of 20°C. The same protocol was repeated. At the end of each period, pressure was recorded and blood samples were taken from the internal carotid artery, external jugular vein, and femoral vein catheters. The returned blood flow from the aorta, superior vena cava (SVC), or inferior vena cava (IVC) was measured directly. The cerebral tissue blood flow was also measured at the same time. The auditory brainstem responses were monitored with Neuropack 4 (MEM-4104; Nippon koden, Tokyo, Japan).

Analysis

The blood samples were drawn into heparinized syringes, immediately placed on ice, and subsequently analyzed at 37°C for pH, oxygen tension, carbon dioxide tension, oxygen saturation, oxygen content, total carbon dioxide, hematocrit, and hemoglobin with ABL-300 (Radiometer, Copenhagen, Denmark). The cerebral tissue blood flow was measured with RBF-2 (Biomedical Science) using the hydrogen clearance method. The cerebral tissue blood flow was calculated, subtracting that at total circulatory arrest.

Calculations

Vascular resistance (R) was calculated using this formula: $R = 79920 \times (Pa - Pv)/Q$ ($dynes \cdot s \cdot cm^{-5}$), where Pa is arterial pressure, Pv is venous pressure, and Q is returned blood flow (mL/min). Oxygen consumption ($\dot{V}O_2$) was calculated by the equation: $\dot{V}O_2 = (O_2CTf - O2CTr) \times Q/100$ (mL/min), where O_2CTf is oxygen content of perfused blood. O_2CTr is oxygen content of returned blood, and Q is returned blood flow. Exudation of carbon dioxide ($ExCO_2$) was calculated using this formula: $ExCO_2 = (tCO_2r - tCO_2f) \times Q/1{,}000$ (mmol/min), where tCO_2f is carbon dioxide of perfused blood, tCO_2r is carbon dioxide of returned blood, and Q is returned blood flow (mL/min).

Results were expressed as the mean value and standard deviation. Statistical significance was determined by the paired *t* test.

Results

Return Blood Flow

During CPB, a third of the perfused blood was returned through the SVC and the rest was returned through the IVC. During RCP, 20% of the blood perfused through the SVC was returned through the aorta and the rest drained through the IVC (Fig 2).

Pressure

During RCP at 300 mL/min the external jugular venous pressure was about 25 mm Hg, which was 5 to 10 mm Hg higher than the carotid arterial pressure or the femoral venous pressure (Fig 3).

Vascular Resistance

The vascular resistance between the aorta and SVC did not change significantly from CPB to RCP 300 at both normothermia and hypothermia. The vascular resistance between the SVC and the IVC was lower than that

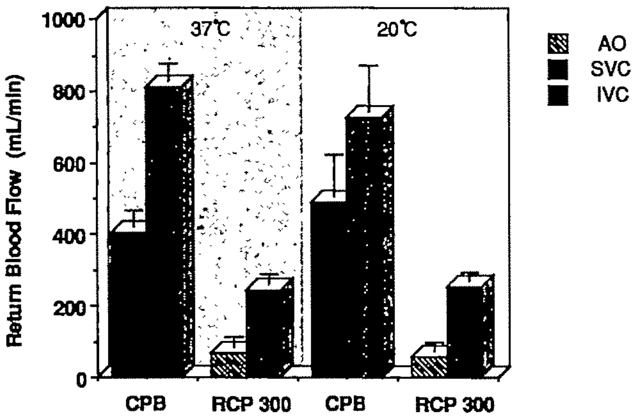

Fig 2. Returned blood flow rate through the aorta (AO) *and superior vena cava* (SVC) *during cardiopulmonary bypass at 1,200 mL/min* (CPB) *and through SVC and inferior vena cava* (IVC) *during retrograde cerebral perfusion* (RCP) *at 300 mL/min.* Shaded area *is normothermia and* white area *is hypothermia.*

between the SVC and aorta during RCP 300 ($p < 0.05$) only at normothermia (Fig 4).

Cerebral Blood Flow

Retrograde cerebral perfusion of 300 mL/min provided half of the cerebral blood flow of the control CPB at both normothermia and hypothermia. The cerebral blood flow decreased as the SVC flow rate decreased. Retrograde cerebral perfusion at 200 mL/min provided about 30% and RCP 100 provided about 15% of the cerebral blood flow of the control CPB (Fig 5).

Cerebral Vascular Resistance

Cerebral vascular resistance during RCP 300 was significantly lower than that during the control CPB at both normothermia ($p < 0.05$) and hypothermia ($p < 0.01$) (Fig 6).

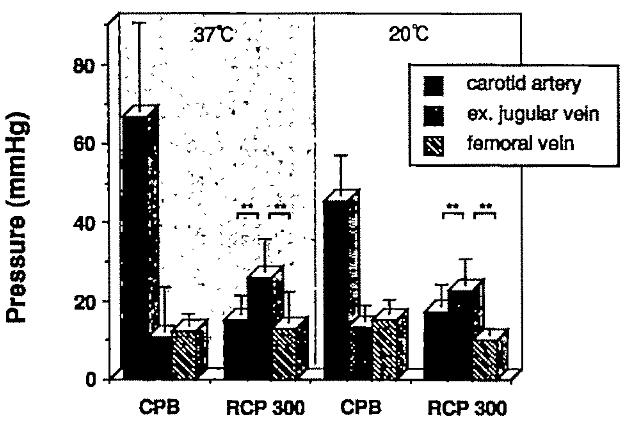

Fig 3. Blood pressure of the internal carotid artery, external jugular vein, and femoral vein during cardiopulmonary bypass at 1,200 mL/min (CPB) *and retrograde cerebral perfusion* (RCP) *at 300 mL/min at normothermia* (shaded area) *and hypothermia* (white area). (***significant difference,* p < 0.01.)

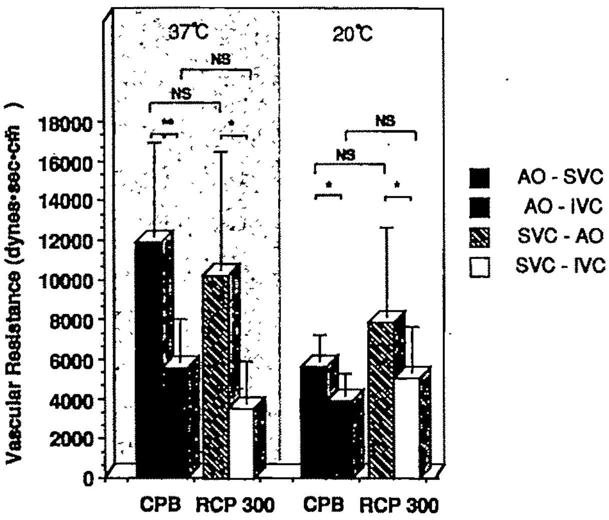

Fig 4. Vascular resistance between the aorta (AO) *and superior vena cava* (SVC) *or inferior vena cava* (IVC) *during cardiopulmonary bypass at 1,200 mL/min* (CPB) *and between SVC and AO or IVC during retrograde cerebral perfusion* (RCP) *at 300 mL/min.* Shaded area *shows values at normothermia and* white area *shows values at hypothermia.* (*p < *0.05;* **p < *0.01;* NS = *not significant.)*

Oxygen Tension of the Returned Blood

The oxygen tension of the blood returned through the aorta during RCP 300 was lower than that of the blood returned through the SVC in the control CPB. The oxygen tension of the blood returned through the IVC during RCP 300 was a little lower than that of oxygenated blood (Fig 7).

Oxygen Saturation of the Returned Blood

The blood returned through the aorta during RCP 300 showed significant desaturation even at hypothermia,

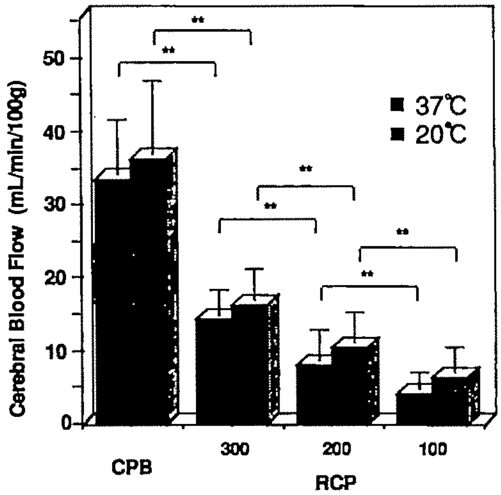

Fig 5. Cerebral blood flow of 100 g wet volume during cardiopulmonary bypass at 1,200 mL/min (CPB) *or retrograde cerebral perfusion* (RCP) *at 300, 200, or 100 mL/min. A* black column *shows cerebral blood flow at normothermia and a* striped column *shows that at hypothermia.* (***significant difference,* p < *0.01.)*

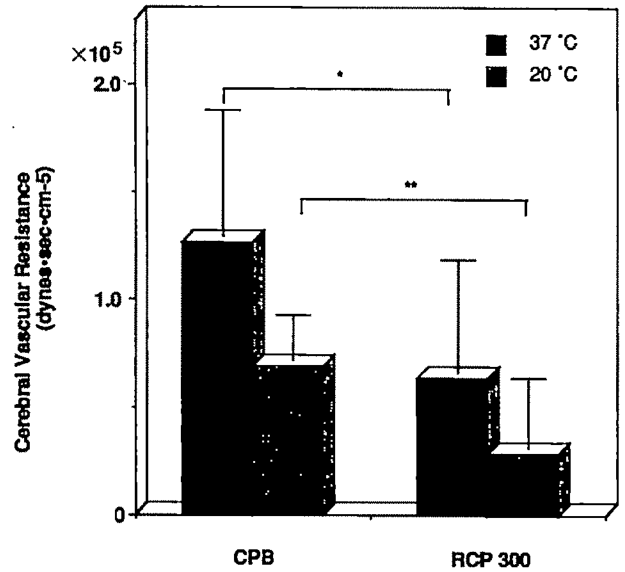

Fig 6. Cerebral vascular resistance during cardiopulmonary bypass at 1,200 mL/min (CPB) or retrograde cerebral perfusion (RCP) at 300 mL/min. A black column *shows cerebral vascular resistance at normothermia and a* striped column *shows that at hypothermia. (*$p < 0.05$; **$p < 0.01$.)*

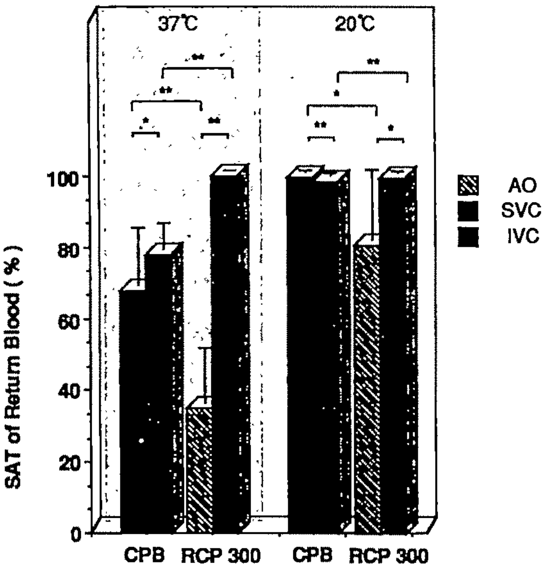

Fig 8. Oxygen saturation (SAT) of blood returned through the superior vena cava (SVC) and the inferior vena cava (IVC) during cardiopulmonary bypass at a flow rate of 1,200 mL/min (CPB) and that through the aorta (AO) and IVC during retrograde cerebral perfusion at 300 mL/min (RCP 300). Shaded area *shows saturation at normothermia and* white area *shows that at hypothermia. (*$p < 0.05$; **$p < 0.01$.)*

whereas the blood returned through the SVC during control CPB showed little desaturation at hypothermia. The blood returned through the IVC did not show desaturation even at the normothermia (Fig 8).

Oxygen Consumption

At normothermia, the $\dot{V}O_2$ calculated from the blood returned through the aorta during RCP 300 was a third of the $\dot{V}O_2$ in the SVC area during CPB. The $\dot{V}O_2$ calculated from the blood returned through the IVC during RCP 300 was only 7% of the $\dot{V}O_2$ in the IVC area during CPB. Whole-body oxygen consumption during normothermic RCP 300 was 15% of that during normothermic CPB. On the other hand, at hypothermia the $\dot{V}O_2$ calculated from the blood returned through the aorta during RCP 300 also was a third of the $\dot{V}O_2$ in the SVC area during CPB, but the $\dot{V}O_2$ calculated from the blood returned through the IVC during RCP 300 was a third of the $\dot{V}O_2$ in the IVC area during CPB. Therefore, whole-body oxygen consumption during RCP 300 at hypothermia was a third of that during CPB at hypothermia (Fig 9).

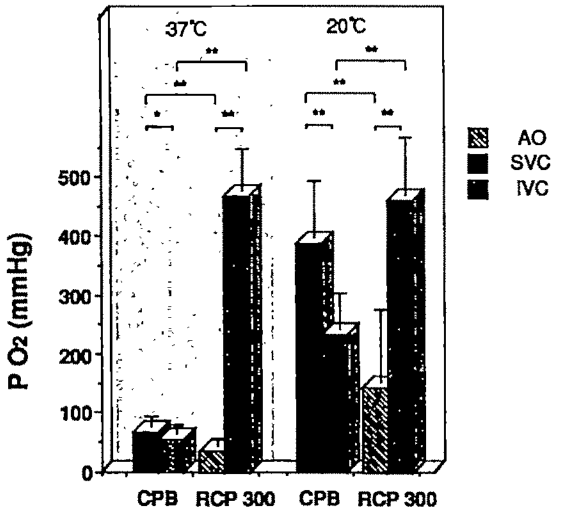

Fig 7. Oxygen pressure (PO_2) of blood returned through the superior vena cava (SVC) and the inferior vena cava (IVC) during cardiopulmonary bypass at 1,200 mL/min (CPB) and through the aorta (AO) and IVC during retrograde cerebral perfusion at 300 mL/min (RCP 300). Shaded area *shows PO_2 at normothermia and* white area *shows that at hypothermia. (*$p < 0.05$; **$p < 0.01$.)*

Exudation of Carbon Dioxide

At normothermia, the EXCO$_2$ into the blood returned through the aorta during RCP 300 was 20% of that into the SVC during CPB, and the EXCO$_2$ into the IVC during RCP 300 was only 6% of that into the IVC during CPB. Whole-body EXCO$_2$ during normothermic RCP 300 was about 10% of that during normothermic CPB. At hypothermia, the EXCO$_2$ into the blood returned through the aorta during RCP 300 was 30% of that into other SVC during CPB, and the EXCO$_2$ into the IVC during RCP 300 was 20% of that into the IVC during CPB. Whole-body EXCO$_2$ during hypothermic RCP 300 was more than 20% of that during hypothermic CPB (Fig 10).

Auditory Brainstem Responses

The auditory brainstem responses disappeared immediately when RCP was applied, but recovered completely as soon as CPB was resumed.

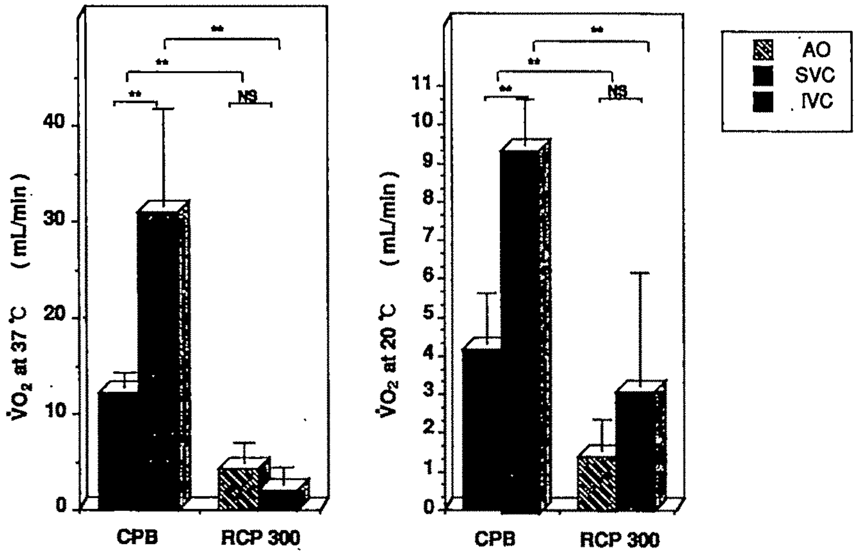

Fig 9. Oxygen consumption ($\dot{V}O_2$) *calculated from blood returned through the superior vena cava* (SVC) *and the inferior vena cava* (IVC) *during cardiopulmonary bypass at 1,200 mL/min* (CPB) *and of blood returned through the aorta* (AO) *and IVC during retrograde cerebral perfusion* (RCP) *at 300 mL/min at normothermia (left) and at hypothermia (right).* (*$p <$ *0.05;* **$p <$ *0.01;* NS = *not significant.)*

Comment

Protection of the brain during interruption of cerebral circulation is most important during aortic arch operations. Deep hypothermic circulatory arrest or isolated cerebral perfusion has been commonly used to protect the brain [1–5]. However, neither technique is entirely satisfactory. Retrograde perfusion through a superior vena caval cannula has been used in the management of massive air embolism during the CPB [10]. The blood perfused through the SVC is returned through the aorta. Retrograde cerebral perfusion through the SVC has also been used during deairing after total circulatory arrest. Hypothermic RCP as a technique for protecting the brain has been reported [6, 7]. Since January 1990 we have applied continuous hypothermic RCP through the SVC without IVC drainage in aortic arch operations.

In our experimental study, cerebral tissue blood flow, vascular resistance, whole-body oxygen consumption and carbon dioxide exudation during RCP were examined in a canine model. Twenty percent of blood perfused through the SVC was returned through the aorta and the rest drained through the IVC. This suggests that some portion of the retrograde-perfused blood runs through the capillary vessels and drains into the artery and the rest runs through veno-venous or veno-capillary-venous connections and drains into the vein. Vascular resistance between the SVC and IVC is lower than that between the SVC and the aorta. This suggests that there are veno-venous shunts between the SVC system and the IVC system. Cerebral vascular resistance during RCP was lower than that during CPB, whereas vascular resistance in the SVC area during RCP (SVC to aorta) was similar to that during CPB (aorta to SVC). This may be due to obstruction to SVC flow related to venous valves in the extremities.

Retrograde cerebral perfusion at 300 mL/min can provide half of the cerebral blood flow of CPB at 1,200 mL/min. In this study cerebral blood flow was measured

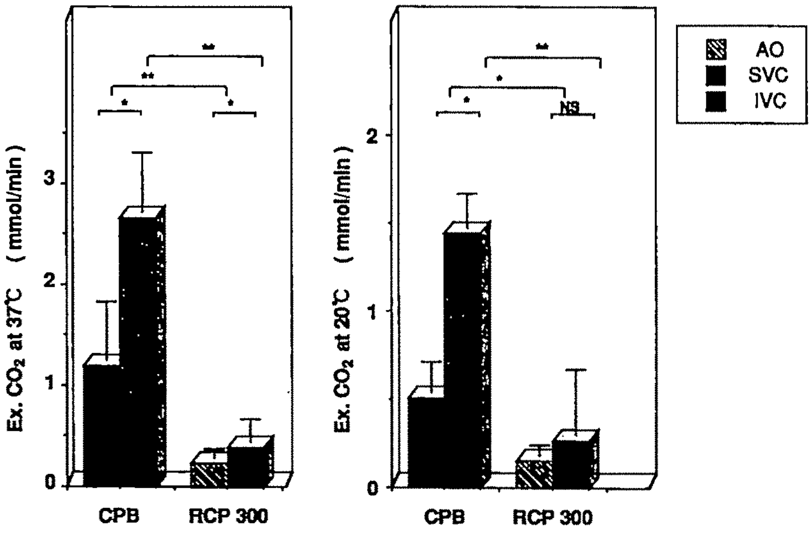

Fig 10. Carbon dioxide exudation ($ExCO_2$) *calculated from blood returned through the superior vena cava* (SVC) *and the inferior vena cava* (IVC) *during cardiopulmonary bypass at 1,200 mL/min* (CPB) *and* $ExCO_2$ *of blood returned through the aorta* (AO) *and IVC during retrograde cerebral perfusion* (RCP) *at 300 mL/min at normothermia (left) and at hypothermia (right).* (*$p <$ *0.05;* **p $<$ *0.01;* NS = *not significant.)*

by the hydrogen clearance method. It has been known that tissue blood flow in gray matter is greater than that in white matter [8, 9, 11]. It is somewhat difficult to obtain accurate intracortical placement of a hydrogen electrode in the dog because the cortex is quite thin. We have placed the electrode obliquely in an endeavor to return it entirely within the cortex and confirmed its depth in histologic sections of the tissue examined.

The hydrogen clearance method measures tissue blood flow, which clears the tissue concentrations of the hydrogen. During RCP, tissue blood flow that runs into the artery was measured, but blood flow that runs through veno-venous connection may also be measured by this method. Therefore, the hydrogen clearance method might overestimate cerebral blood flow during RCP.

Retrograde cerebral perfusion at 300 mL/min can also supply a third of the oxygen provided by CPB at 1,200 mL/min. However, RCP cannot supply enough blood flow and oxygen to maintain all normal cerebral function as evidenced by the loss of normal auditory brainstem responses during normothermic RCP. The remainder of the body was ischemic during RCP. Retrograde cerebral perfusion may, however, reduce ischemic damage of the brain. Whole-body oxygen consumption becomes small as body temperature decreases [12–14]. Deep hypothermia can protect the brain during cerebral circulatory arrest for about an hour [15–18]. Deep hypothermic RCP should extend the possible duration of safe interruption of the cerebral circulation. However, RCP is associated with high venous pressures and may cause brain edema. During circulatory arrest the blood cells cause microaggregation, which may be the genesis of cerebral injury, in the capillaries. Retrograde cerebral perfusion reduces blood cell microaggregation and may reduce cerebral injury.

The dog is not a good model for RCP because the external jugular vein is the main venous system from the brain and also has venous valves, which interfere with retrograde perfusion through the SVC. Primate models are superior for RCP experiments. In our dogs, we bluntly destroyed valves in the external jugular vein with an instrument before the RCP experiments. In humans, there is usually no venous valve in the internal jugular vein, but immature venous valves at the venous angle have been reported [19, 20]. In humans, after initiation of RCP, pump pressure increases abnormally as the flow rate increases. The venous valve should be removed or another method for cerebral preservation should be applied. Otherwise, venous valves that interrupt the retrograde blood flow to the extremities help to concentrate blood flow to the brain.

Retrograde cerebral perfusion is a simple method that may help preserve the brain and extend the duration of safe cerebral circulatory arrest. It requires no need for a clamp or cannula in the cerebral vessels, which provides a better operative field and avoids possible arterial injury.

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DISCUSSION

DR JOHN C. ALEXANDER (Evanston, IL): I congratulate Dr Usui and associates on an interesting and provocative study. They have shown that the brain can be perfused in a retrograde manner through the venous system and I have shown evidence for central nervous system metabolism. My colleagues and I have been interested in the same proposition. We have modified our cardiopulmonary bypass circuit to achieve the same retrograde venous perfusion shown by Usui and associates in a clinical setting.

In our normal bypass circuit, venous drainage and the pump suckers return blood to the reservoir, pump, and oxygenator. Oxygenated blood is returned to the patient by the arterial line. After deep hypothermia of 15° to 18°C is established, flow is reversed. The pump suckers return blood from the field to the reservoir, pump, and oxygenator. Oxygenated blood is returned through the venous line into the right heart. We have not used double cannulation. We have used just a simple two-stage cannula.

Using low flow of 300 to 400 mL/min, we can maintain low but constant flow into the patient. We have been able to achieve retrograde perfusion just as Usui and associates have, as is evidenced by blood coming back out of the cerebral circulation that is unsaturated, as they have shown. We believe this modification of the deep hypothermia technique prevents cerebral air embolization, as well as maintaining central nervous system hypothermia, and may supply the brain with oxygen that is useful. We agree with Usui and associates that the retrograde venous perfusion is interesting and may offer substantial benefit to patients undergoing arch repair.

I had intended to ask Usui and associates if they had tried this clinically. They did not include that in their abstract. It is clear that they have. We would add six additional cases treated with this technique with no neurologic deficit. We have been quite pleased with this and believe that it may indeed offer the missing link to explain some of the problems associated with deep hypothermia that have at this point been a mystery.

DR YUTAKA OKITA (Nara, Japan): I would like to make a comment on the issue of retrograde cerebral perfusion. It echoes our technique of retrograde cerebral perfusion with deep hypothermic system circulatory arrest for surgical treatment of aortic arch aneurysms at Tenri Hospital in Japan. We modified the methods reported by Dr Mills in 1980 and by Dr Lemole in 1982. We have been using this technique in surgical treatment of the aortic arch aneurysms since 1986. Our favorable results in 4 patients were reported in 1987 as a first successful case in Japan, and then we also initiated continuous retrograde cerebral perfusion technique in 1987. We had no neurological sequelae and the recovery of evoked potentials and electroencephalogram was quite satisfactory in 10 patients with continuous retrograde cerebral perfusion.

The difference in oxygen content between perfused blood and the blood draining from the arch vessels at the beginning and after 10 minutes of continuous retrograde cerebral perfusion reflected most likely that this technique provided sufficient metabolic support of the brain during deep hypothermia. These clinical results and details of the method have been already reported in the *Journal of Cardiovascular Surgery, Torino,* by my colleague Dr Ueda, in 1990 [1].

We certainly have been intrigued by the idea and have also conducted a similar series of experiments in 6 mongrel dogs to provide the efficacy of cerebral protection with our continuous retrograde cerebral perfusion technique. One of the problems that has frustrated us is that the external jugular vein is the major drainage route from the brain of the dog and that vein contains many functioning valves that obstruct retrograde perfusion; also, the internal jugular vein, which drains the cerebral venous blood, is very tiny. Our experiment is suspended because the dog is not suitable material for this kind of experiment. We think that the baboon seems to be a good model to get reliable results. According to our experience, your results may be unreliable.

Do you have any comments on this?

DR JULIE A. SWAIN (Las Vegas, NV): Dr Mike Crittenden in our laboratory at the National Institutes of Health performed a similar study with 2 hours of circulatory arrest in sheep with both antegrade and retrograde cerebroplegia. He showed that with retrograde cerebroplegia we got virtual brain death, or very poor protection, with a long period of circulatory arrest. With your 1 hour of circulatory arrest, one can expect reasonably good results with many methods of cerebral perfusion. My concern is with your cerebral oxygen consumption data.

Dr Fox at the University of Alabama laboratory a decade ago showed preservation of oxygen consumption at flow rates that are probably essentially equivalent to these. You show a decrease in oxygen consumption. You are postulating that it is due to a decrease in oxygen delivery, although I think you do have adequate delivery. I wonder if, in fact, you have a decline in oxygen use due to neurologic damage. Your clinical results are excellent, but this might be secondary to the mechanism suggested by Dr Alexander.

DR USUI: Thank you for your comments. Dr Okita, I agree with your comment. The dog is not so good a model for this kind of experiment because the dog has venous valves, which interrupt retrograde perfusion, at the external jugular vein. We destroyed these valves before the experiment, but in some dogs we could not achieve adequate blood flow. We excluded these dogs from this study. Clinically, we have to mention that 80% of humans have venous valves at the venous angle. Most of these valves are not competent, but in some cases they interrupt retrograde perfusion. So when we can not get adequate blood flow, we have to change from retrograde cerebral perfusion to another method. Dr Swain, at this time we do not have enough data to answer your question, but I think that retrograde cerebral perfusion can supply the oxygen to the brain and it may be beneficial in protecting the brain.

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Laryngotracheal Resection and Reconstruction for Subglottic Stenosis

Hermes C. Grillo, MD, Douglas J. Mathisen, MD, and John C. Wain, MD

General Thoracic Surgical Unit, Massachusetts General Hospital, and Department of Surgery, Harvard Medical School, Boston, Massachusetts

Eighty patients with inflammatory stenoses of the subglottic larynx and upper trachea were treated by single-stage laryngotracheal resection and reconstruction. Fifty stenoses originated from postintubation lesions (endotracheal tubes, tracheostomy, cricothyroidostomy), 7 originated from trauma, 19 were idiopathic, and 4 were miscellaneous. Repair consisted of resection of the anterolateral cricoid arch in all patients, plus resection of posterior laryngeal stenosis where present, with salvage of the posterior cricoid plate, appropriate resection and tailoring of the trachea, and primary anastomosis using a posterior membranous tracheal wall flap to resurface the bared cricoid cartilage in 31 patients. One postoperative death resulted from acute myocardial infarction. Long-term results were excellent in 18 patients, good in 48, satisfactory in 8, and failure in 2. Three additional patients had good results at discharge but were followed up for less than 6 months.

(Ann Thorac Surg 1992;53:54–63)

Inflammatory stenosis of the upper trachea that also involves the subglottic larynx cannot be treated by simple circumferential resection because this would destroy the function of the recurrent laryngeal nerves. Many procedures, often complex and multistaged, have been devised to solve this problem [1]. In an effort to improve the often indifferent results obtained by such operations, single-stage procedures involving partial resection of the subglottic larynx and immediate plastic reconstruction by varying techniques have evolved. Systematic approaches to this problem have been made by Ogura and Roper [2], Gerwat and Bryce [3], Pearson and associates [4], Couraud and colleagues [5], and Grillo [1]. All reported surprisingly good results using single-stage plastic procedures.

We describe here our experiences in treating 80 consecutive patients in whom the subglottic larynx was partially resected with trachea for inflammatory stenotic processes and in whom primary reconstruction was performed. The anterior cricoid arch was resected in all patients. The technique of operation was previously described [1].

We have excluded cases of laryngotracheoplastic resection done for primary and secondary tumors [6, 7] because we believe that the problem is a very different one. In inflammatory disease, whatever the cause, the process frequently extends above the stenosis in the subglottic larynx, nearly to the vocal cords. Resection, therefore, cannot be carried proximally to include all of the inflammation. Standardized operative techniques that remove the anterior subglottic larynx and also excise scar circumferentially posteriorly are applicable to these patients. In contrast, in those patients with tumors, resections are individualized for the specific location of the tumor and frequently are done in the presence of unilateral paralysis of a recurrent laryngeal nerve; most importantly, once excision of tumor has been accomplished, the line of anastomosis lies in normal tissues. This almost guarantees success in procedures performed for tumors [6, 7].

Material and Methods

Characteristics of Patients

Fifty of the 80 patients had lesions that resulted from intubation done for ventilatory support in all but 1 (Fig 1). Thirty-one of these had endotracheal tubes only; in 16 the lesion was believed to result from stomal erosion of the cricoid cartilage, and in 3 the originating trauma was an elective cricothyroidostomy for ventilatory support. In 7 patients the stenosis was of traumatic origin. In 4 of these it was due to blunt trauma, usually with separation of larynx and trachea and with injury to the lower larnyx, and in 1 it was due to gouging of the anterior laryngotracheal wall by a flying object. A patient suffering from an inhalation burn was the first treated in this series. One patient was referred from another institution with a postoperative stenosis after an attempt at a complex laryngotracheal repair with a hyoid graft, performed to correct deformity due to goiter.

Of the 23 remaining patients, 19 had idiopathic laryngotracheal stenosis (Figs 2, 3). One patient had localized amyloid disease. Two had a long history of stenosis commencing with diphtheria in childhood (Figs 4, 5). Whether successive intubations and tracheostomies contributed to or actually initiated stenosis was impossible to determine. One patient had clinical stigmata of relapsing polychondritis. One patient with stenosis after endotracheal intubation and ventilation was believed to suffer

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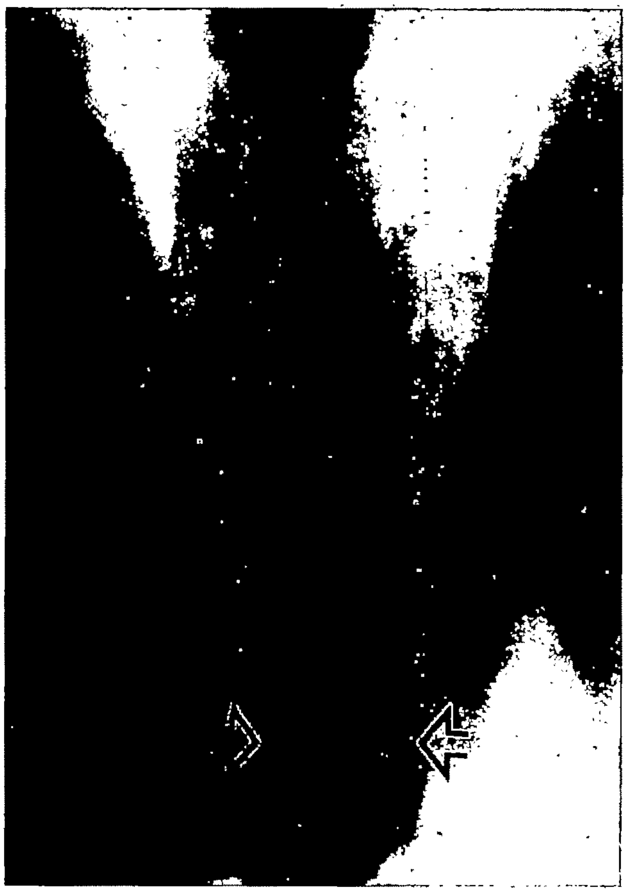

Fig 1. Tomogram showing stenosis of the subglottic larynx and upper trachea resulting from ventilation through an endotracheal tube. Below the asymmetric vocal cords lies a small "atrium" of subglottic larynx just above the stenosis. The airway achieves normal diameter at the level of the open arrows. *In this patient the lesion was extended by multiple laser treatments and by a tracheostomy done in conjunction with that treatment.*

from a poorly defined connective tissue disease. An additional patient with similar stenosis was an achondroplastic dwarf.

All patients with postintubation stenoses except 1, whether from endotracheal tubes alone or from tracheostomy tubes, were referred from other institutions. This made it impossible to gather precise information on the circumstances of intubation and, in particular, on the size and type of tubes used, as well as data about cuff inflation pressures. It was our clinical impression that many of the male patients with lesions resulting from endotracheal intubation were of small stature and hence had tracheas of similar diameter. They may well have been intubated with larger tubes. It is also possible that some of the patients with eroded cricoid cartilages in relation to their tracheostomy stomas had also suffered from prior circumferential damage from an endotracheal tube cuff. It was not possible in every case to sort this out from available history or from pathological findings. The original diseases for which intubation and ventilation were used presented a usual spectrum. These included intracranial trauma, Guillain-Barré syndrome, multiple sclerosis, seizure disorder, acute cardiac disease, post–cardiac surgical support, respiratory failure from obstructive pulmonary disease, pneumonia in the presence of leukemia, asthmatic crisis with bronchospasm, allergic respiratory arrest, postabdominal surgical complications, toxic ingestion, and postesophagectomy respiratory failure.

Forty-nine of the 80 patients were female. This preponderance reflects the fact that 18 of 19 patients with idiopathic stenosis were female. The traumatic stenoses resulted from cable injury in 2, steering wheel injury in 1, hanging in 1, and a flying object in 1. All were young and male. The ages of the patients ranged from 11 to 85 years, with an even spread in the second through eighth decades (n = 11–14) except for the fifth decade (only 3 patients). One patient was 85 years old.

Many patients, of course, suffered from systemic diseases such as arteriosclerotic heart disease, diabetes mellitus, and chronic obstructive pulmonary disease. Five patients had tracheoesophageal fistulas when first seen. In 2 the fistula had resulted from blunt trauma and in 3 from intubation and ventilation with tracheoesophageal erosion (Figs 6–9). In 16 patients, paralysis or paresis of one or both vocal cords was identified preoperatively. In numerous others there was malfunction of one or both vocal cords.

Most postintubation patients and many others had undergone varied treatment before referral. At least 8 and probably many more had undergone multiple dilations. Forty-two of the patients had a tracheostomy in place upon arrival. The tracheostomy had either been placed for management of the stenosis or could not be removed because of the stenosis. An additional 2 had had prior tracheostomy which had been removed. At least 5 were treated with dilation and T tubes before referral. More than 10 patients had single or multiple laser treatments. Fulguration and cryosurgery were also used. In a number of patients, local and systemic steroids had been used. One patient received 4,000 cGy of irradiation in a misguided attempt to reduce scar tissue.

More important from the standpoint of a potential surgical procedure were prior failed attempts in 23 patients to correct the stenosis or injury by open operation. These attempts had been of wide variety, including laryngotracheal resection and reconstruction, interposition of hyoid bone graft, laryngofissure with excision of scar, cutaneous or mucosal graft with stenting, Rethi procedure, cutaneous reconstruction, closure of tracheoesophageal fistula, and numerous additional procedures directed to the glottic aperture itself. Some had at least three open surgical attempts before referral.

All patients were evaluated by systematic radiological studies [8], including fluoroscopic examination of vocal cord function (see Figs 1–9).

Operative Correction

In 9 patients surgical correction was delayed after referral for the following reasons: initial glottic repair (including arytenoidectomy and cord lateralization), 4; subsidence of local inflammation, 2; weaning from steroids, 2; and

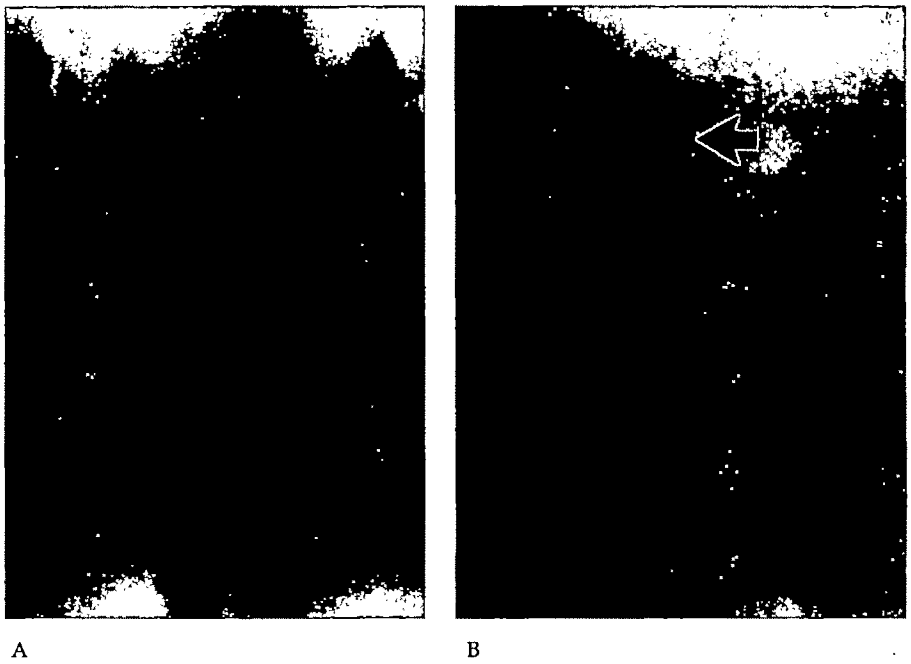

Fig 2. Idiopathic laryngotracheal stenosis. (A) Tomogram showing the vocal cords, a somewhat narrowed immediate subglottic larynx, and maximal stenosis below this. (B) Postoperative roentgenogram of trachea, with filter. The arrow *is at the glottic level. The anastomosis between the slightly narrowed larynx and the trachea is widely patent.*

observation for progression of idiopathic stenosis, 1. Three patients with bilateral vocal cord paralysis had cord lateralization done. Seven others with unilateral paralysis had an adequate glottic aperture.

All patients underwent bronchoscopy under general anesthesia, most often immediately before resection and reconstruction, using rigid bronchoscopes and magnifying telescopes. Anesthesia was induced by inhalation, using either a face mask or a flexible endotracheal tube placed in an existing stoma. If a stoma was available, no effort was made to dilate the proximal stenosis, because the resulting trauma can make identification of the lesion more difficult. Where no stoma was present, gentle dilation was carried out to a point sufficient to avoid hyper-

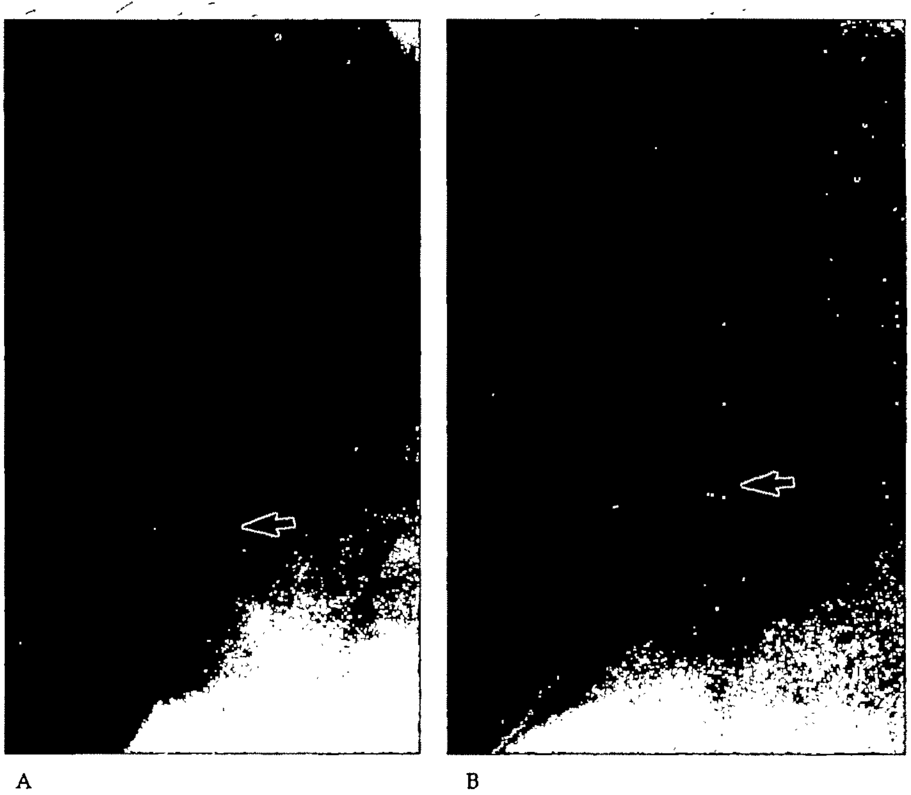

Fig 3. Lateral views of the airway of the patient from Figure 2. (A) Preoperative view. (B) Postoperative roentgenogram. Arrows *indicate the anterior and posterior walls of the airway at the stenotic and anastomotic levels, respectively.*

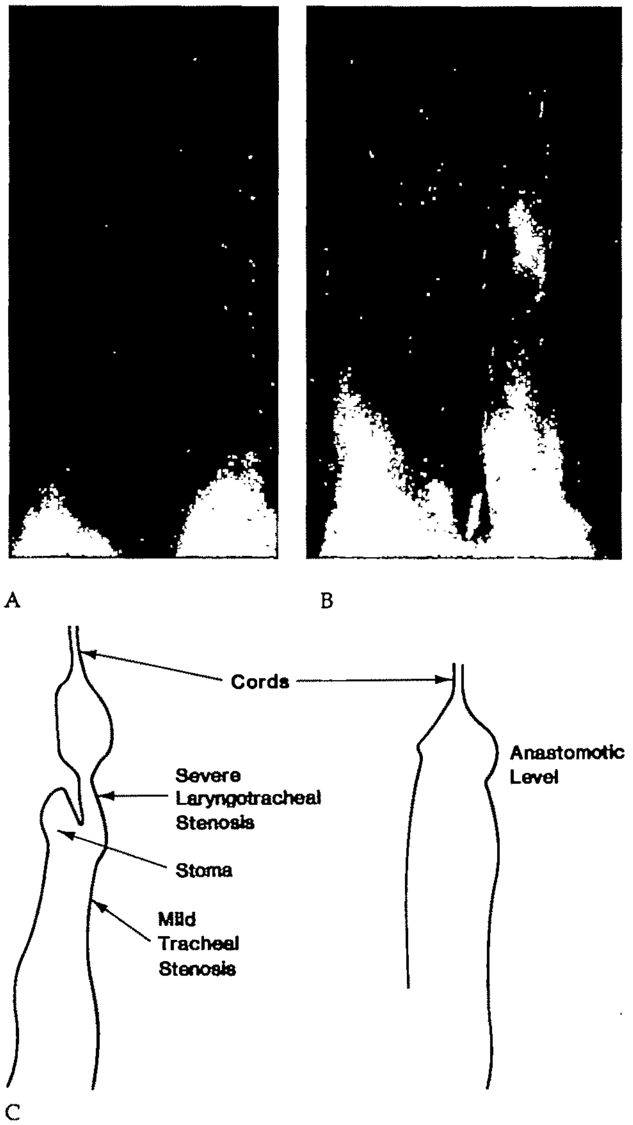

Fig 4. Roentgenograms of a patient who had diphtheria at age 2 years and carried a tracheostomy until age 7 years. At age 68 years he was discovered to have an impossibly tight stenosis for intubation for coronary artery bypass grafting and had emergency tracheostomy. (A) Tomogram showing tight glottic aperture, stenotic immediate subglottic larynx, exceedingly tight stenosis below this, and a relative stenosis in the upper trachea. The patient had one paralyzed vocal cord and both anterior and posterior commissural stenoses with, however, a functional glottis. (B) Postoperative tomogram. The subglottic larynx has been widened by the tracheal anastomosis. A posterior membranous tracheal flap was used. (C) Tracings from the roentgenograms to clarify the anatomy.

carbia and potential arrhythmia, but not beyond that. A small-diameter endotracheal tube (No. 5 or 6) was accepted for the initial phase of the operation.

Operative approach was through a cervical collar incision in all but 2 patients, who required upper sternal division through a short vertical limb. If the level was appropriate, an existing stoma was excised through the center of the collar incision. In the 43 patients in whom a stoma was present, 40 stomas were excised with the resected specimen, one was used postoperatively for a temporary tracheostomy and later allowed to close, and two, more remote from the stenotic segment, were closed surgically at the time of resection.

The length of resection measured between 1.5 and 6.5 cm, with most falling in the range of 2.0 to 4.5 cm. Only 1 patient had a resection of 1.5 cm, and 9 had resections greater than 4.5 cm. In 7 patients, a Montgomery suprahyoid release [9] was performed to relieve tension on the anastomosis.

In those patients in whom the stenotic process involved only the anterior portion of the subglottic larynx, resection of this portion of the cricoid arch in an arcuate line extending up to a point just short of the midline of the thyroid cartilage anteriorly sufficed. The posterior margin of resection was along the lower border of the cricoid cartilage [1]. This series does not include patients who merely had a partial resection of the lower margin of the anterior cricoid cartilage. In patients in whom the subglottic process was circumferential, extending in front of the posterior plate of the cricoid, the line of posterior mucosal resection was incised above the level of stenosis, approaching the arytenoid cartilages. All involved mucosa and scar tissue was excised from the front of the posterior cricoid plate, leaving the cartilage intact posteriorly, to be surfaced by a broad-based flap of membranous trachea advanced from below (Fig 10). The margin of the anterior defect in the subglottic larynx was sutured in both types of resection to a prow-shaped segment of one distal tracheal ring, shaped to fit. The details of this operation have been described previously [1]. The posterior membranous flap of tracheal wall was required for resurfacing of the bared cricoid in 31 patients. In 49 it was possible to perform an anastomosis without resecting the tissues overlying the posterior cricoid plate. Mucosal anastomoses were performed in 75 patients with 4-0 Vicryl sutures. The 5 earliest cases were anastomosed with 4-0 Tevdek.

In the 5 patients with tracheoesophageal fistula, including 1 with three adjacent fistulas, the esophagus was closed in two layers with inverting sutures, and a pedicled flap of strap muscle was interposed between the esophageal closure and the laryngotracheal anastomosis anteriorly [10]. Three of these patients had undergone prior attempts at closure of the fistula, with multiple attempts in 2.

Because most of the patients had inflammation of the subglottic larynx extending above the area of maximum stenosis, which often reduced the potential for correction to 50% or less of normal cross-sectional area at that level, and because of our fear of postoperative glottic edema, we initially planned to place a small tracheostomy tube distal to the anastomosis quite routinely (or an endotracheal tube where the distal trachea was inaccessible for tracheostomy). It became evident that an accessory airway was necessary only in those patients whose airway was of borderline adequacy immediately after operation. In the first 20 patients, tracheostomy was used in 14 at the time of the original operation and an endotracheal tube in 1. In

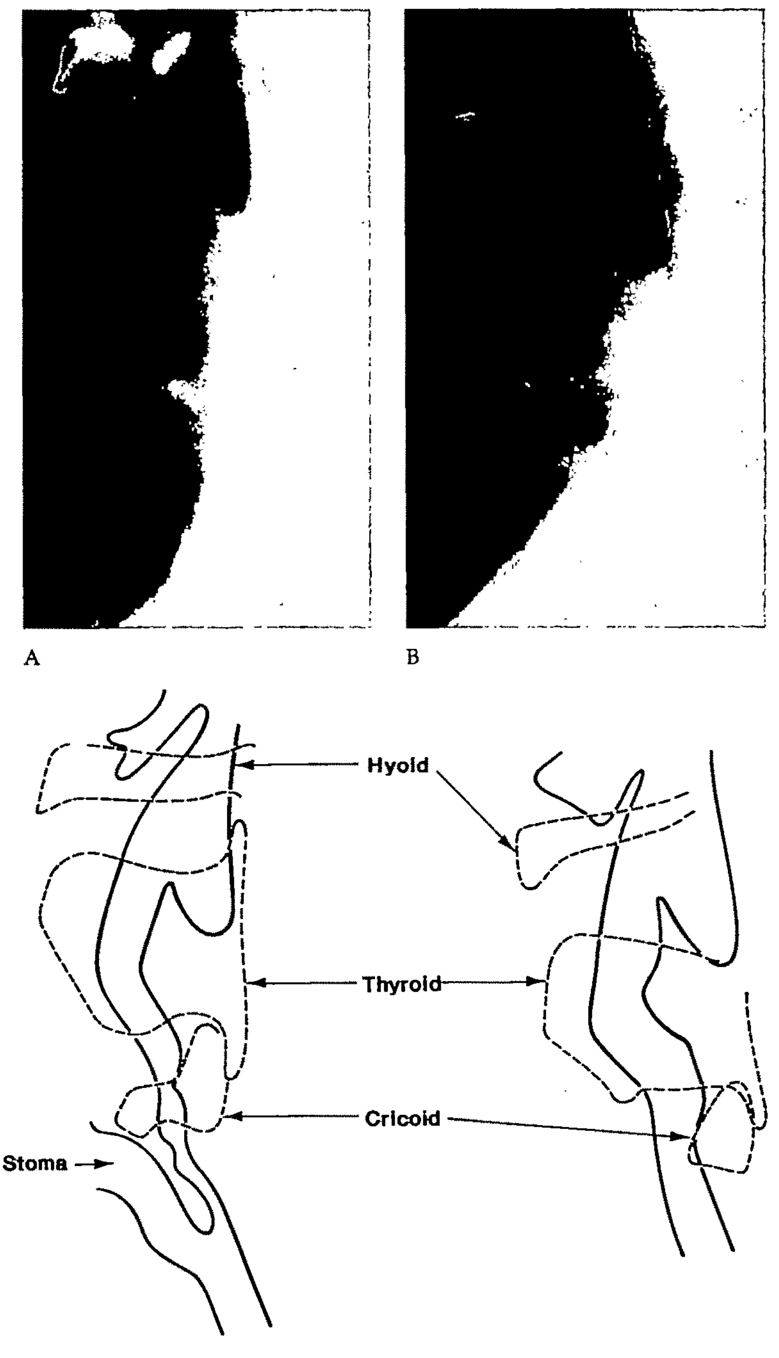

Fig 5. Lateral roentgenograms of patient from Figure 4. (A) A tight and irregular stenosis may be traced through the subglottic larynx past the distorted and calcified cricoid cartilage. The stomal tract may be seen eroding against the cricoid margin and further deforming the subglottic larynx and upper trachea. (B) The reconstructed airway. (C) Tracings of the lateral airway preoperatively and postoperatively to clarify the anatomy. Dotted lines *indicate cartilaginous outlines. The* solid lines *trace the airway margins.*

the subsequent 60 patients, tracheostomy was used only nine times. This represented a drop in use of protective airway devices from 75% to 15%. A postoperative airway was required for less than a month in 14 patients (average, 10 days; median, 8 days) and between 1 and 12 months in 10 patients (average, 4 months; median, 3 months). One patient was decannulated after 3 years, and 2 remain intubated.

Results

One postoperative death occurred in a 66-year-old woman with severe heart disease who had incurred a stenosis from an endotracheal tube placed for the management of a stormy course after coronary artery bypass grafting in another institution. She suffered a fatal myocardial infarction immediately postoperatively. Two patients suffered early and long-term failure of treatment. One was the only male patient who was retrospectively classified as having idiopathic laryngotracheal stenosis. He underwent prior resection and reconstruction at another institution. Stenosis recurred after our reconstruction also. He carries a permanent tracheostomy and has rejected any further attempt at reconstruction. The other patient had had a tracheostomy in infancy and had undergone multiple

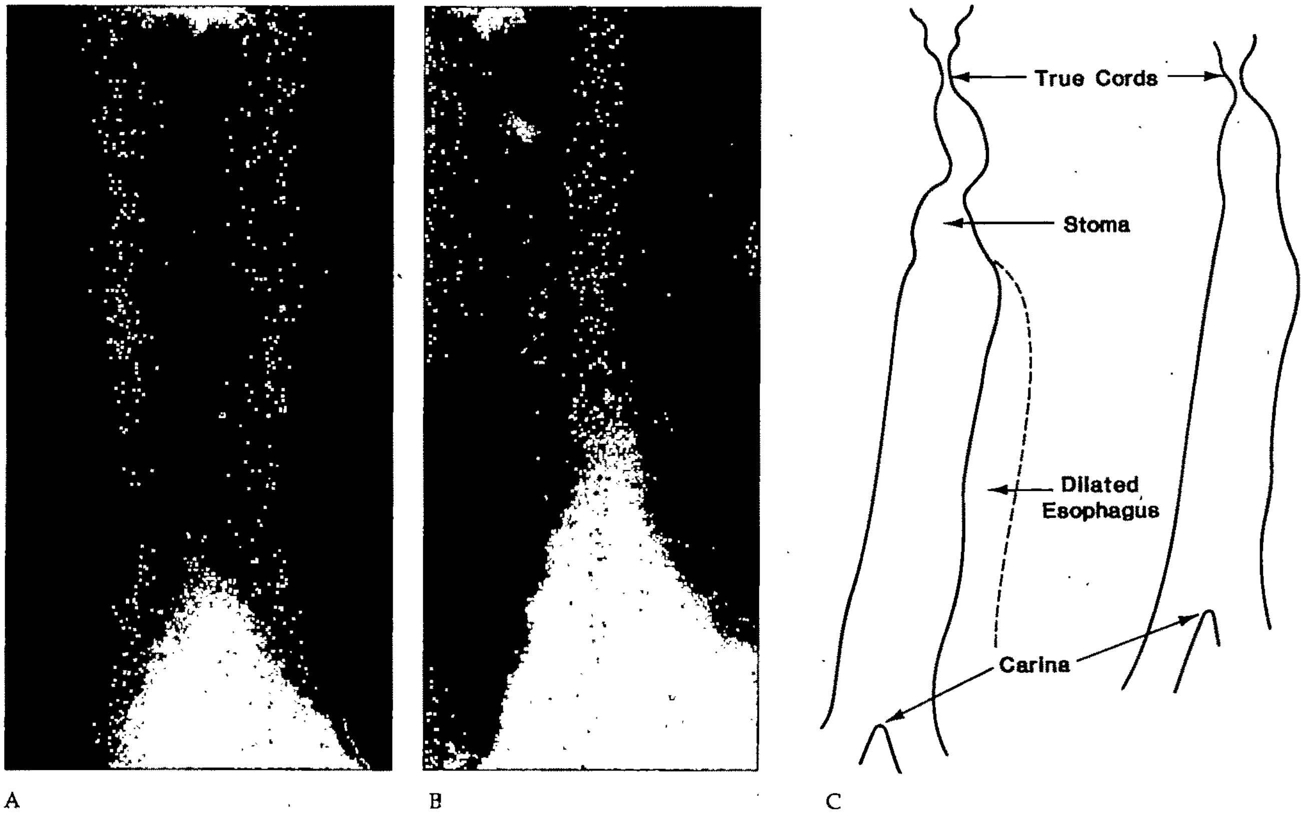

Fig 6. Patient with laryngotracheal stenosis and tracheoesophageal fistula resulting from prolonged ventilation with an endotracheal tube, followed by a tracheostomy and with subsequent erosion to produce a fistula. Prior attempts to close the fistula surgically had failed. The left vocal cord was paralyzed and the right moved poorly. (A) Anteroposterior roentgenogram of the larynx and trachea showing immediate subglottic narrowing with severe stenosis in the larynx below this. The esophageal dilation commencing at stomal level is characteristic. (B) Postoperative view. The anastomosis is widely open. (C) Tracings of roentgenograms (A, B) to clarify the radiologic anatomy.

reconstructions and T tube splinting before attempted repair here. Her tracheal process continues to require a T tube. One patient who had an early failure of operation was decannulated successfully after nearly 3 years. She was the first patient in the series who was operated on for stenosis that followed a severe inhalation burn. We have since preferred to treat burn injury of the upper airway by prolonged T tube splinting. The hypertrophic nature of burn scar endangers early surgical reconstruction. One patient had successful repair of a laryngotracheal stenosis but years later required a tracheostomy for progressive distal chondromalacia related to her achondroplasia.

In classifying the results obtained, we have deemed as *excellent* a normal voice and no limitation of respiration at rest or on exercise. Patients were considered to have a *good* result if they suffered only slight lessening of maximum volume of voice, slight hoarseness that did not impede vocal use, slight weakness of voice after prolonged use, diminished ability to sing, and adequate breathing for all normal activities. Patients labeled as having a *satisfactory* result were those with a hoarse voice and either slight wheezing or shortness of breath on exercise, not sufficient to impair usual activities. Eighteen patients achieved an excellent result, 48 a good result, and 8 had results classified as satisfactory. As noted, there were two failures and one immediate postoperative death. Three patients are listed as uncertain despite initial good results because their follow-up was for less than 6 months.

Late deaths from other causes included heart disease in 2 patients, pneumonia in chronic lymphatic leukemia, gastrointestinal carcinoma in 3, and neurologic death in 1. These deaths were recorded between 4 months and 9⅔ years after operation. Forty-nine patients were contacted in late 1990 in follow-up from 6 months to 12 years. In 13 additional patients, follow-up was available for between 2 and 10 years after operation, and in 4 for between 1 and 2 years. In 3, follow-up data were available at between 6 months and 1 year, and in 3 less than 6 months. To be emphasized is the fact that no patient who achieved an excellent or good status was found to deteriorate in subsequent months or years. In contrast, an apparent failure improved over 3 years, as noted earlier, and most who required tracheostomies eventually were successfully decannulated. It may be concluded that, if anything, the long-term results indicated represent a minimum statement.

Early complications, in addition to the need for prolonged intubation due to glottic edema or anastomotic edema, included superficial wound infection that re-

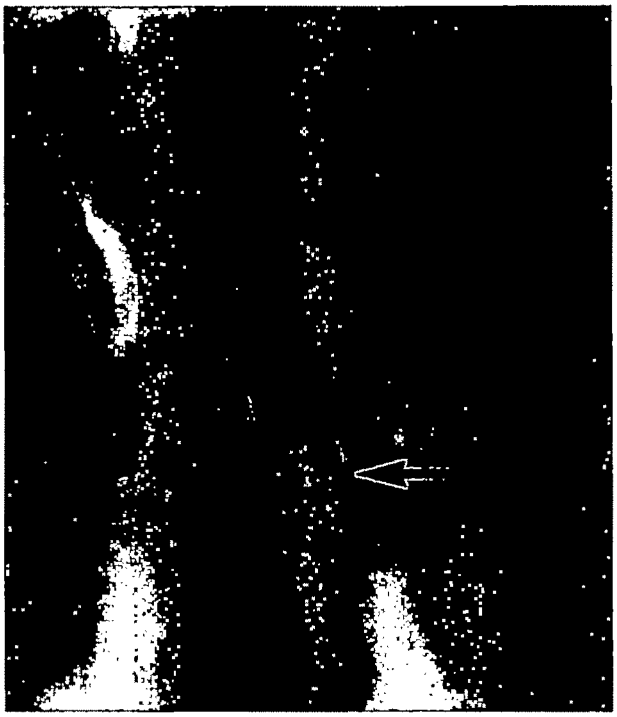

Fig 7. Tomographic detail of the lesion shown in Figure 6A. The arrow *indicates the point of maximum stenosis.*

quired drainage in 1 patient, suture granuloma in the incision that required removal of the suture in a second patient, and reexploration for air leak in 1 patient. A pinhole leak was closed with a local muscle flap and healed promptly. Eight patients had difficulty with deglutition or with aspiration postoperatively. All had undergone extensive resection, and 4 of them had suprahyoid laryngeal release performed. One required a gastrostomy tube for treatment and 2 others had such tubes placed at the time of operation in anticipation of difficulty, especially as 1 of these 2 had also undergone reclosure of a recurrent tracheoesophageal fistula. With time and retraining in swallowing, it was possible to remove all gastrostomy tubes. Tracheal granulations were removed bronchoscopically in 2 patients who had anastomoses performed with Tevdek and in 5 who had anastomoses performed with Vicryl. One of these patients has restenosis. A polyp of the vocal cord was treated by laser in 1 patient. The patient with leukemia required a prolonged period for healing of the tracheal stoma, which had been made at the time of reconstruction. Twenty-two patients had a persistent hoarse voice in varying degrees and 16 had weakness of the voice when attempting to project their speech. In 4 patients, these were expected consequences of bilateral vocal cord paralyses due to trauma, and in some others, of unilateral paralyses that were preexistent. Eight complained of an alteration of singing voice.

Comment

Otolaryngological literature is filled with descriptions of multiple modes of treatment of nonneoplastic stenosis involving subglottic larynx and upper trachea [1]. Conservative measures include dilation, intubation, stenting, steroid injection, cryotherapy, electrocoagulation, and laser therapy. Operative procedures, often complex, include scar excision, incision of cricoid anteriorly or posteriorly, grafts of buccal mucosa or skin, free cartilage inserts, pedicled hyoid grafts, and creation of cutaneous gutters variously supported—all often stented for a prolonged period and usually accompanied by tracheostomy. More procedures than encouraging results have been recorded.

Conley [11] in 1953 noted a single instance of posterior cricoid resection for tumor to the "inner surface of the thyroid cartilage," thus preserving the recurrent laryngeal nerves and suturing "mucoperichondrium" of the trachea over the cricoid bed. He commented, "It is perhaps a procedure that should be used more often in surgery on the trachea," but he believed resection of trachea must be limited to two rings. In 1961, Shaw and associates [12] resected cricoid and performed tracheal anastomosis successfully, but this was in patients with recurrent laryngeal nerve palsy after trauma. Ogura and Roper [2] in 1962 detailed a single-stage procedure for infraglottic stenosis, resecting the anterior and lateral cricoid and the inferior portion of the posterior cricoid. Their initial 3 patients with posttraumatic stenosis all had paralyzed cords. In subsequent reports, Ogura and Powers [13] emphasized subperichondrial resection of the stenosis from posterior cricoid to preserve recurrent laryngeal nerve function, and Ogura and Biller [14] in 1972 noted success in 14 of 17 patients so treated for chronic subglottic stenosis. All patients had accompanying thyrohyoid laryngeal release, anastomotic stenting, and protective tracheostomy.

Gerwat and Bryce [3] in 1974 reported good results in 4 patients who underwent oblique resection of anterior and lateral cricoid to the cricothyroid joints. Stenosis had resulted from tracheostomy, probable endotracheal intubation, trauma, and unknown cause. Thyrohyoid release was used in all and visualization of recurrent nerves advised. Pearson and co-workers [4] added partial subperichondrial resection of the posterior cricoid to remove posterior stenotic scar, narrowed the trachea by suturing the ends of cartilage together, and intussuscepted the trachea into the groove created by the subperichondrial resection. A follow-up report [15] in 1986 of 21 patients with nonneoplastic stenosis (postintubation, traumatic, burn, and idiopathic) and 7 with neoplasm so treated produced a good airway in 26 and limitation in 2. A T tube was used postoperatively in 10, and 13 had laryngeal release. Couraud and associates [16] updated their experience between 1978 and 1988 with laryngotracheal resection for stenosis resulting from intubation or trauma, including 27 patients who had a Pearson-type procedure and 7 who had total or subtotal cricoid plate resection with stenting. All had good results.

The initial report by Grillo [1] in 1981 described 16 good or excellent results in 18 patients with nonneoplastic laryngotracheal stenoses treated by our variation of oblique resection of cricoid, adding a membranous tracheal wall flap to resurface cartilage where scar had been

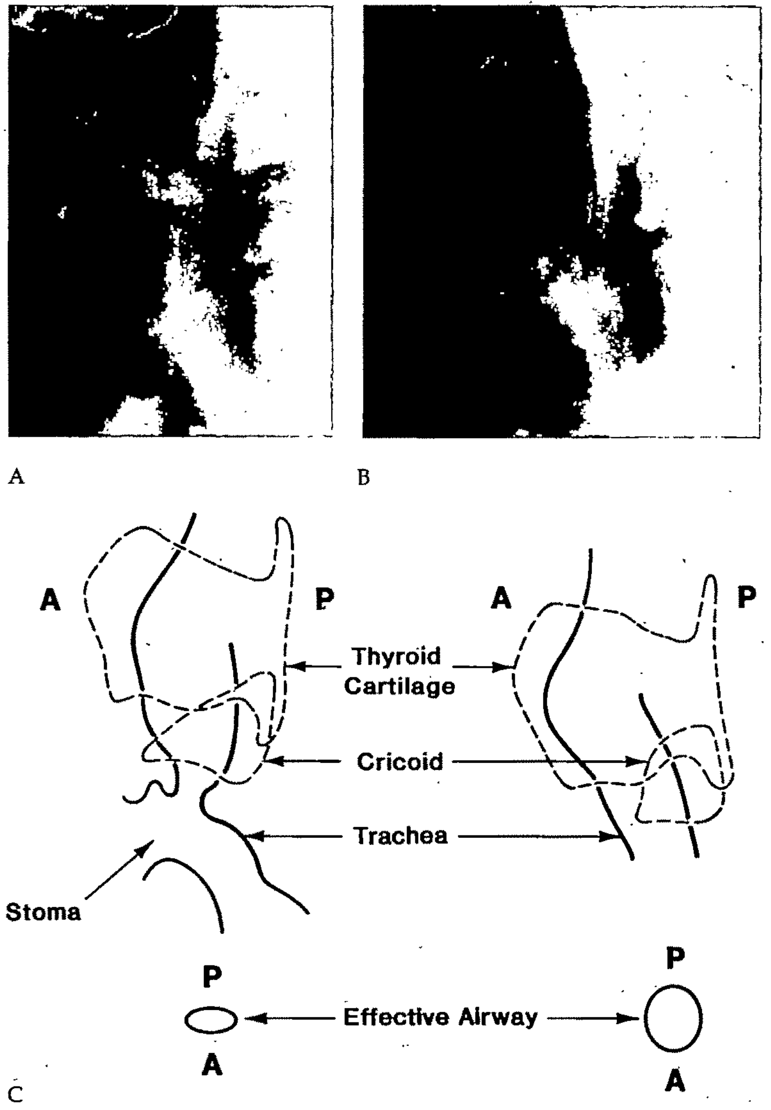

Fig 8. Lateral views of larynx and trachea corresponding to Figure 6. (A) Preoperative. (B) Postoperative. (C) Diagrams of the roentgenographic anatomy. Solid lines *trace the airway.* Dotted lines *outline the cartilages. The effective airways, preoperatively and postoperatively, are constructed from measured diameters in the roentgenogram.*

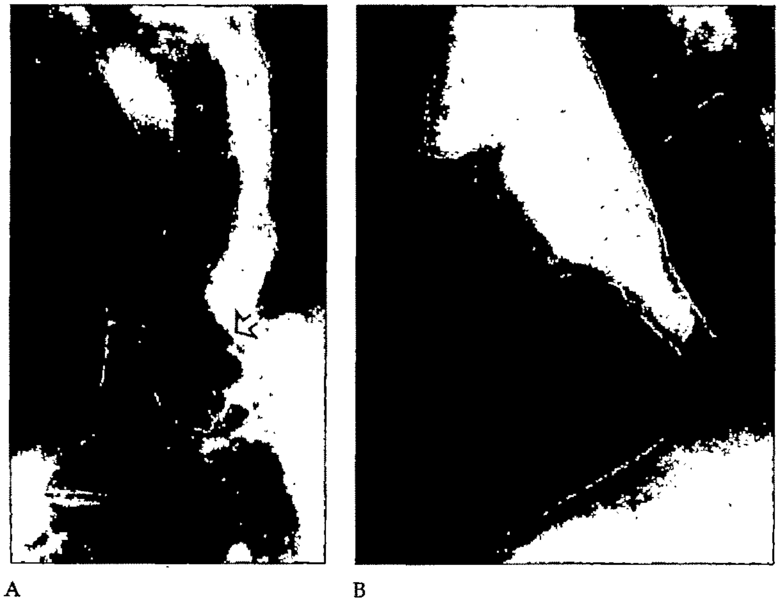

Fig 9. Barium studies showing (A) the tracheoesophageal fistula and (B) the postoperative repaired trachea and esophagus. The open *arrow in (A) points to the fistula.*

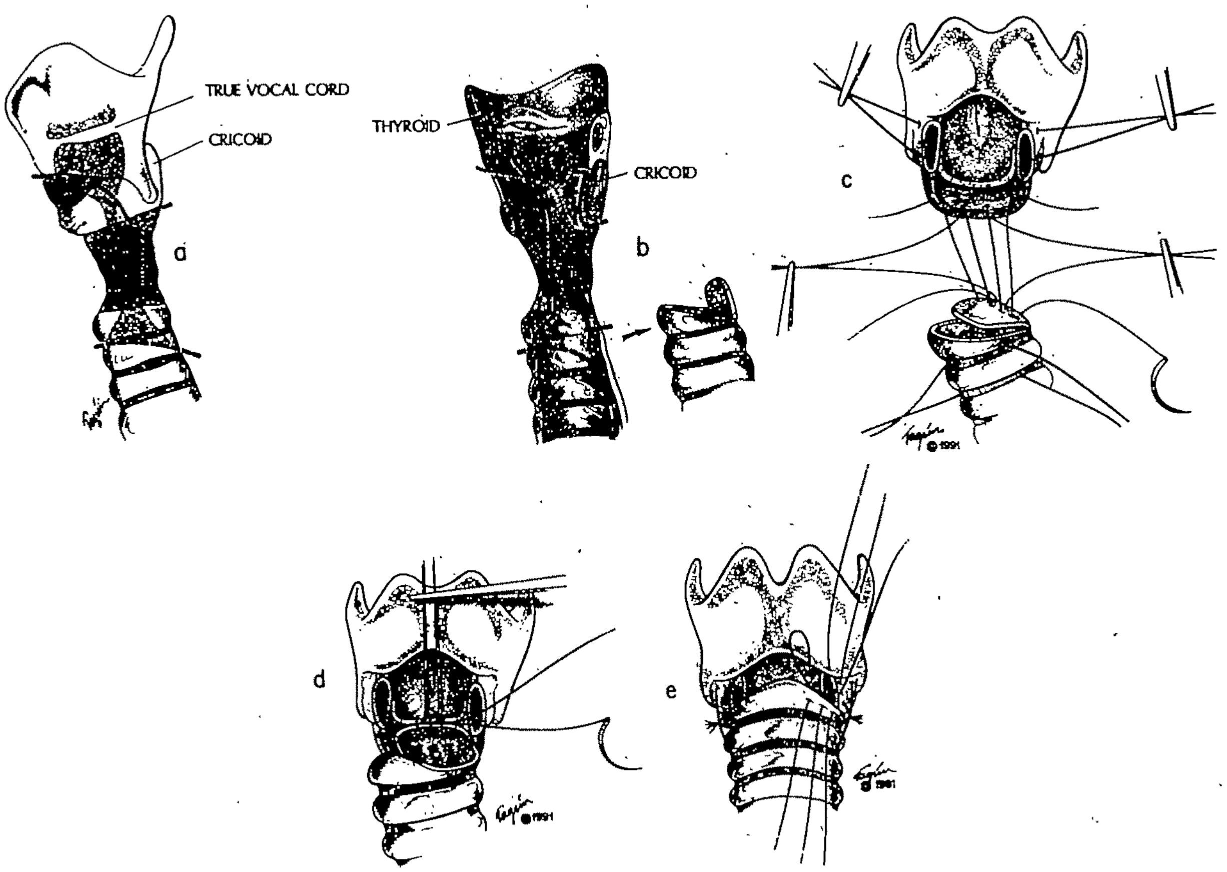

Fig 10. Technique of laryngotracheal resection and reconstruction. (a) external lines of division of the larynx and trachea are indicated by dashed lines. The anterior cricoid arch is removed. (b) When the subglottic intralaryngeal stenosis is circumferential, scar is removed from the front of the posterior cricoid lamina, baring the cartilage, as shown. The residual posterior cricoid lamina protects the recurrent laryngeal nerves. Distally, the trachea is beveled over the length of one cartilage, as shown, to fit the anterolateral subglottic defect that has been created. A broad-based flap of membranous tracheal wall is fashioned to resurface the bared cricoid plate. (c) The posterior flap is fixed to the lower margin of the cricoid plate with four extraluminal sutures (4-0 Tevdek). The lateral traction sutures (2-0 Vicryl) are also shown in the larynx proximally and in the trachea distally. (d) Posterior mucosal anastomotic sutures (4-0 Vicryl) are placed with knots to lie behind the mucosa. Traction sutures are omitted in this diagram for simplicity. (e) After placement of all the posterior and posterolateral anastomotic sutures as far anteriorly as the lateral stay sutures, the patient's neck is flexed, the stay sutures are tied, the external fixing Tevdek sutures are tied, and then the posterior mucosal sutures. The anterior and anterolateral anastomotic sutures are then placed and finally tied serially. (Figures a and b are reproduced with permission from: Grillo HC. Primary reconstruction of airway after resection of subglottic laryngeal and upper tracheal stenosis. Ann Thorac Surg 1982;33:3–18.)

excised from the front of the posterior cricoid lamina. The series has now grown to 80 patients and results continue to be encouraging, as described here.

The similar and generally good results obtained in this difficult group of patients by units employing similar single-stage operations suggest that many complex procedures still used might well be abandoned. However, diagnostic precision is essential, operative timing must be carefully judged, operative technique is exacting, and postoperative care early and late must be meticulous. These are not operations to be done occasionally.

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DISCUSSION

DR JOEL D. COOPER (St. Louis, MO): Before congratulating Dr Grillo and his co-workers, I would like to be excused a moment of personal nostalgia. Dr Grillo, it was 25 years ago last month that as a resident I was stimulated by you to undertake a study of the causes of postintubation tracheal stenosis, and that tutelage of yours kindled an interest in airway problems that has persisted over 25 years. I might point out, however, that neither of us has gotten very far since those days of working on the complications of tracheostomy together. You have managed to go upstream about 4 cm now, as you have worked on subglottic problems, and we have gone downstream about 8 cm working on problems of bronchial anastomosis. But it has been great fun.

I do want to congratulate Dr Grillo and his co-workers on this very important presentation. To me the most important aspect is that it reflects very well the methodical, the careful, the systematic, very meticulous approach that is so characteristic of Dr Grillo and his work, and it is this type of systematic approach that allows the transmittal of this rather uncommon type of procedure across the country and around the world to those who have an interest in surgery of the airway. It is too bad, that the ear, nose, and throat surgeons have not caught on a little bit more, and then you would not have to see so many patients who have had preliminary procedures before hand.

To me there were several features of this current update that were important: the consistent, good results and the fact that the results do not deteriorate. If anything, they get better with time. I think that is another important message of the current presentation by you and your group.

I would like to ask you just a few questions. You mentioned the level to which you go. I know you are familiar with the work of Dr Couraud, who has done some anastomoses to the vocal cord or perhaps even above the vocal cord, and I would like to ask you your opinion. Have you had any experience with lesions at that particular level? In the same vein, I have occasionally used a laryngofissure to get high up in the larynx, though I suspect with your flap modification you can do the posterior anastomosis more simply at a higher level. But I did want to know whether you ever employed a laryngofissure to complement this particular procedure.

Also, you and I have discussed over the years the potential perils of cricothyroidotomy, and yet your group has recently presented a series of safe, postoperative cricothyroidotomies with the use of the minitracheostomy and I would like to know your current views on that procedure, particularly with reference to injury in the subglottic region.

Finally, regarding the mysterious disease of idiopathic subglottic stenosis, of which I believe you had a very large series here, 18 or 19, do you have any clues as to what is causing that very unusual condition, which so often is thought to be a malignancy until multiple biopsies fail to reveal its origin?

Once again thank you very much for the privilege and opportunity of discussing this presentation.

DR GRILLO: I must thank Dr Cooper for his insightful comments. He was one of the originators of what we call the Toronto procedure, so he is as familiar as anyone with this problem.

I have mixed feelings about the otolaryngologist not taking this procedure on. We have encouraged them to do so. I share a mixed feeling of regret that they do not do it but perhaps a little pleasure that they leave it to thoracic surgeons who perhaps do anastomoses of this type better.

We have gone higher and higher in the larynx as the years have gone by, up to just below the arytenoids, but I have not resected the vocal cords or gone up to the supraglottic larynx as Louis Couraud has done. I am very much aware of his excellent and very interesting work. I simply have left supraglottic and glottic problems to the otolaryngologists. We often examine these patients endoscopically just before operation in association with a senior otolaryngologist. If the larynx is stenosed right up to the vocal cords, correction is usually done by the otolaryngologist. Tracheal repair is performed subsequently, usually in a separate stage. Laryngofissure has not been necessary with this exposure because you can reach way up, basically to the arytenoids.

I still deplore elective cricothyroidostomy. I know statistically you can get away with it most of the time, but it is a deliberate insult to the larynx. Although stenosis from a deliberate insult to the trachea—tracheostomy—is usually correctable the first time around, some injuries to the larynx are uncorrectable at the outset; they simply cannot be straightened out. This is too big a price to pay for a dubious gain. Minitracheostomy, on the other hand, is done through a very small incision in the cricothyroid membrane. As you know, Dr John Wain in our institution has followed up these cases carefully and simply has not seen any serious injuries.

We report 19 patients with idiopathic stenosis at the laryngotracheal level. We have quite a few others at lower levels, tracheal and carinal. The diagnosis is by exclusion, and I am not sure all cases are of the same origin. They have been studied very carefully by the pathologists and by other diagnostic techniques. We do not have final answers. A more detailed discussion of this problem was offered in an abstract submitted for this meeting, but because it was not accepted, you will have to wait for another year to hear the rest!

Neutrophils Are Not Necessary for Ischemia-Reperfusion Lung Injury

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The role of neutrophils (PMNs) in ischemia-reperfusion injury after lung transplantation is unclear. If PMNs are involved in ischemia-reperfusion injury in the intact rat, then PMNs should sequester in the injured lung and PMN–depleted rats should develop less injury. Group A rats were treated with a rabbit anti-rat PMN antibody causing profound neutropenia (<100 PMNs/μL) and group B with control serum (>2,000 PMNs/μL). Rats were anesthetized and left lung ischemia was sustained for 90 or 180 minutes by clamping the bronchus and the pulmonary artery and vein. Lung injury was quantified by the accumulation of radiolabeled (^{125}I) albumin in ischemic left and nonischemic right lungs (cpm per gram of lung/cpm per gram of blood): Ischemia caused significant lung injury ($p < 0.05$) in both PMN-depleted (albumin leak index: 90 min, 0.208; 180 min, 0.218) and nondepleted (90 min, 0.222; 180 min, 0.241) animals compared with nonischemic controls (depleted: 90 min, 0.050; 180 min, 0.100; nondepleted: 90 min, 0.063; 180 min, 0.101); microscopy also demonstrated lung injury. The injury was not associated with PMN sequestration as shown by light microscopy. Thus, we conclude that PMNs are not necessary for ischemia-reperfusion injury and PMN-depletion does not attenuate ischemia-reperfusion injury.

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To investigate the mechanism of ischemia-reperfusion (I-R) injury of the lung our laboratory used an ex vivo rat lung model. This technique was shown to be a sensitive and reproducible method to quantitate injury and permit the evaluation of simple interventions for other types of lung injury [1, 2]. Hypothermia was the first variable studied using this model for I-R injury. It was shown that preservation for up to 24 hours of ischemia with uniform hypothermia at 4°C caused no significant injury over control lungs continuously perfused and ventilated. In addition, ventilation without perfusion significantly attenuated I-R injury [3]. Next, the role of circulating blood elements in the pathogenesis of injury was investigated. Lungs were rendered ischemic by stopping ventilation and perfusion at room temperature for 45 minutes. Lung injury occurred when lungs were reperfused with physiologically balanced salt solution (PSS-Ficoll) and was quantitated by the accumulation of radiolabeled iodine-125 bovine serum albumin (^{125}I-BSA) into lung parenchyma and alveolar lavage fluid during reperfusion. Reperfusion with whole blood or PSS-Ficoll supplemented with human or rat neutrophils did not enhance injury, when compared with controls, and significantly reduced injury when compared with lungs reperfused with only PSS-Ficoll. Furthermore, during ischemia, the presence of neutrophils did not enhance injury. Toxic oxygen metabolites were involved in the injury as the addition of erythrocytes or catalase to the perfusate diminished the injury [4]. The lack of augmentation of the lung injury by the exogenous neutrophils added to the reperfusate was not the result of their inability to cause injury because injury could be induced by the addition of phorbol myristate acetate to the reperfusate.

The role of neutrophils in the formation of I-R injury in the ex vivo model markedly differed from work using in vivo models described by others [5, 6]. The absence of injury with neutrophils or whole blood reperfusion in the isolated rat lung model may be species specific or secondary to the lack of neutrophil-stimulating factors present in an in vivo animal. This present study was designed to establish a reliable and reproducible in vivo rat lung model for I-R injury and to investigate the necessity of neutrophils in the formation of this injury.

Material and Methods

Animal Model

Pathogen-free male Long-Evans rats (200 to 300 g; Charles River Laboratories and Harlan Laboratories) were used for all experiments. The experimental protocols were in compliance with the University of Michigan Committee on the Use and Care of Animals. Animals were anesthetized by intraperitoneal administration of 20 mg/kg of pentobarbital and intramuscular administration of 60 mg/kg of ketamine hydrochloride. All animals received intramuscular atropine at 0.5 mg.

Tracheostomy was performed and the animals were

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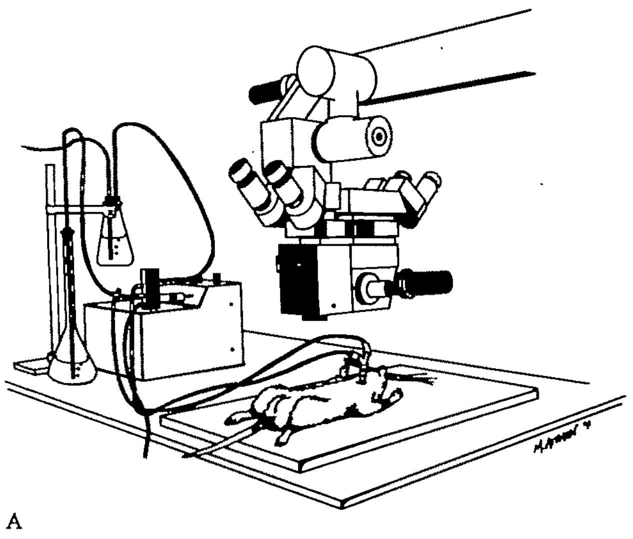

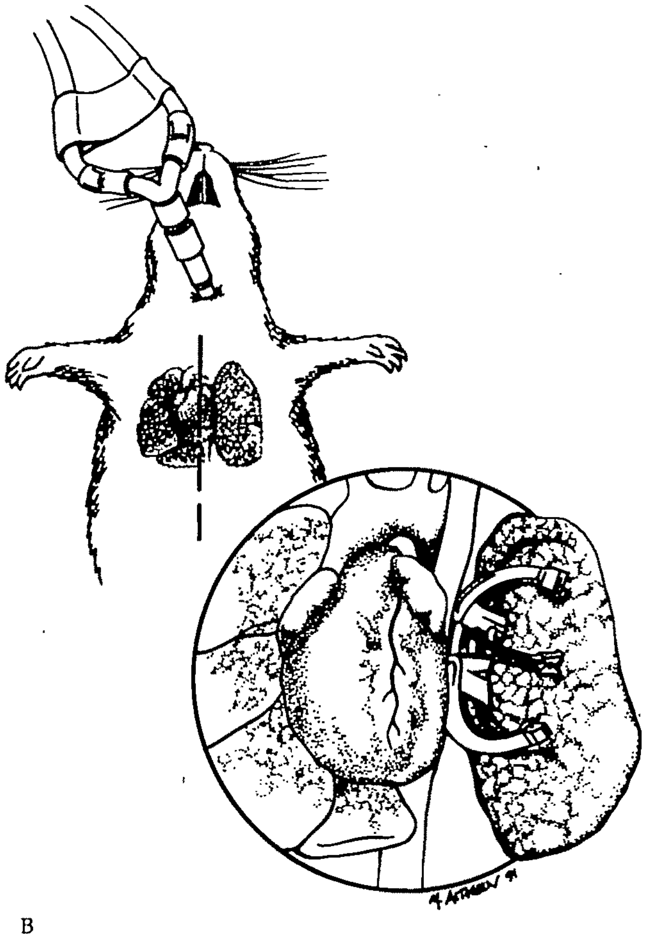

Fig 1. Experimental setup. (A) Rats undergo tracheostomy and are maintained on a rodent ventilator with humidified room air. Dissection is performed under an operating microscope. (B) The left hilar structures are isolated and noncrushing Heifitz clamps are used to prevent perfusion or ventilation.

placed on a Harvard rodent ventilator with room air at 70 cycles per minute, 9 cm H_2O peak pressure, and 2 cm H_2O positive end-expiratory pressure. For experiments with ischemic times of 90 minutes or less the chest wall was sharply removed, whereas for those with ischemic times of greater than 90 minutes, a left thoracotomy was performed to maintain hydration and body temperature. Upon opening, the inferior pulmonary ligament was divided and the left hilum was stripped of all neural, vascular, lymphatic, and connective tissues, thereby isolating the pulmonary artery, vein, and bronchus. All dissection was performed under magnified vision (Zeiss operating microscope). Unilateral left lung ischemia was achieved by complete occlusion of the pulmonary artery, vein, and bronchus using noncrushing Heifitz microvascular clamps (Fig 1). A warming mattress was used to maintain body temperature throughout the experiment. The lungs were kept moist by intermittent application of warm 0.9% normal saline solution. Periods of ischemia ranged from 30 to 180 minutes. At the end of ischemia, the clamps were removed and the lungs were reperfused for 30 minutes. Animals were killed by exsanguination at designated times and the lungs and blood were obtained immediately for analysis as outlined below. Time-matched control animals (shams) underwent identical procedures except the Heifitz clamps were not applied.

Neutrophil Depletion

Depletion of neutrophils from the rats was accomplished using a rabbit anti-rat polymorphonuclear (PMN) antibody (Accurate Chemical and Scientific). A blood sample was obtained from each animal before injection and total white blood cell count was determined using unopettes and a hemocytometer. A blood smear was also taken and stained for white blood cell count and a differential count was obtained by direct microscopic examination. The animals were then injected intraperitoneally with 1 mL of the antibody preparation. After 24 hours, blood samples were again obtained for white blood cell count and differential count. Control animals were treated with rabbit serum that did not contain the anti-PMN antibody. All animals then underwent ischemia and reperfusion as described above.

Experimental Analysis

CONTRIBUTION OF BRONCHIAL AND PULMONARY CIRCULATION ON LUNG BLOOD FLOW. To differentiate the contributions of the bronchial versus pulmonary blood flow to the lung, a color change technique was used. Five groups were studied:

Group 1: no dissection was performed, no clamps were applied (n = 2)

- Group 2: the neural, lymphatic, vascular and connective tissues were left intact but the entire hilum was clamped (n = 4)
- Group 3: the left hilum was stripped of all neural, lymphatic, vascular and connective tissue; the pulmonary artery, pulmonary vein, and bronchus were clamped (n = 4)
- Group 4: the left hilum was again stripped but only the pulmonary artery and pulmonary vein were clamped (n = 4)
- Group 5: no dissection was performed; clamps were individually placed on the pulmonary artery and pulmonary vein but not the bronchus (n = 4)

Animals were injected intravenously with 2 mL of disulfine blue 6.2% dye, which was circulated for 30 minutes. The lungs were observed for change in color representing the presence of perfusion. A change in lung color from pink to blue with the great vessels clamped was taken to indicate the presence of bronchial or collateral circulation.

ROLE OF ISCHEMIA-REPERFUSION INJURY. To determine the effects of I-R injury on lung parenchyma we varied the time intervals of ischemia (without ventilation or perfusion) and divided the animals into four groups. Each group had a different ischemic interval and all groups underwent 30 minutes of reperfusion with ventilation. There were 8 animals in each experimental group. The ischemia times were: group I, 30 minutes; group II, 60 minutes; group III, 90 minutes; group IV, 120 minutes; and group V, 180 minutes. Within each group an equivalent number of time-matched control animals (shams) was included.

Ischemia was produced by stripping the lung of all neural, vascular, lymphatic, and connective tissues. The pulmonary artery, vein, and bronchus were then clamped. The sham animals had the exact surgical procedure without clamping the pulmonary artery, vein, and bronchus but maintained ventilation and perfusion for the respective time spans. After reperfusion with ventilation, injury was assessed by ^{125}I-BSA leak index and histologic examination.

ROLE OF NEUTROPHILS IN ISCHEMIA-REPERFUSION INJURY. For the determination of the role of neutrophils in I-R injury, we compared animals depleted and not depleted of neutrophils at 90 and 180 minutes of ischemia (n = 8 for all groups):

- Group 1A: neutrophil-depleted animals, 90 minutes without ventilation and perfusion followed by 30 minutes of ventilation and perfusion
- Group 1B: as for group 1A but not neutrophil-depleted animals
- Group 2A: neutrophil-depleted animals, 180 minutes without ventilation and perfusion followed by 30 minutes of ventilation and perfusion
- Group 2B: as for group 2A but not neutrophil-depleted animals

All animals underwent ^{125}I-BSA analysis as well as histologic examination.

Quantitative Analysis

A variety of quantitative methods was employed to assess the injury in each group. These methods were as follows:

MICROVASCULAR PERMEABILITY ASSESSMENT. To quantitate microvascular permeability ^{125}I-BSA capillary leakage was measured. Radiolabeled ^{125}I-BSA (prepared by the standard chloramine-T method [1]) with added disulfine blue dye was injected intravenously 15 minutes before the termination of each experiment. Circulation into the previously ischemic left lung was confirmed by color change caused by the disulfine dye. At sacrifice, 1 mL of blood was aspirated from the inferior vena cava. The heart and lungs were removed en bloc and approximately 20 mL of sterile saline was gravity-infused (10 cm H_2O pressure) through the right ventricle to flush out residual blood containing ^{125}I-BSA from the pulmonary vasculature. Both lungs and the blood sample were then weighed and placed in a gamma scintillation counter. The ratio of tissue to blood counts per minute was calculated and normalized by the respective weights of each. The resulting leak index provided a reliable quantitative method for assessing lung microvascular permeability [2].

MORPHOLOGIC ANALYSIS. Light microscopy was performed by inflating the lungs with formalin after the reperfusion period. Samples were processed for light histology. After staining with hematoxylin and eosin, 20 high-power fields (HPFs) per specimen were examined with light microscopy for intraalveolar hemorrhage (red blood cell–filled alveoli/HPF) and for the presence of polymorphonuclear cells (PMNs/HPF).

Electron microscopy was also performed. Additional rats underwent the standard ischemic protocol. Upon sacrifice, the lungs were inflated with 4% glutaraldehyde buffered with sodium cacolydate. Sections (1 mm) were obtained from both lungs and embedded in Spurr's ma-

Table 1. Role of Bronchial Circulation in Rat Lung Perfusion

		Color Change	
Group	Type	Right Lung	Left Lung
1	Sham (no dissection, no clamps) (n = 2)	Yes	Yes
2	Vessels and bronchus clamped; no dissection (n = 4)	Yes	No
3	Vessels and bronchus clamped; hilum stripped (n = 4)	Yes	No
4	Vessels clamped; bronchus not clamped; hilum stripped (n = 4)	Yes	No
5	Vessels clamped; bronchus not clamped; hilum not stripped (n = 4)	Yes	Yes (delayed)

Table 2. Leak Index Values of Experimental Groups With Varying Times of Ischemia

Group	Times (ischemia/ reperfusion)	Left Lung	Right Lung	N
I	30/30	0.085 ± 0.014	0.056 ± 0.011	8
	0/60	0.080 ± 0.011	0.053 ± 0.012	6
II	60/30	0.189 ± 0.029[a]	0.094 ± 0.02	8
	0/90	0.058 ± 0.015	0.055 ± 0.019	6
III	90/30	0.214 ± 0.023[a]	0.089 ± 0.010	22
	0/120	0.073 ± 0.010	0.086 ± 0.012	14
IV	120/30	0.253 ± 0.038[a]	0.116 ± 0.023	8
	0/150	0.068 ± 0.018	0.094 ± 0.022	6
V	180/30	0.368 ± 0.055[a]	0.079 ± 0.05	9
	0/210	0.118 ± 0.037	0.099 ± 0.02	7

[a] $p < 0.05$ compared with internal controls or time-matched shams.

terial. After being stained with toluidine blue, the specimens were examined by light microscopy. Electron microscopy was performed on ultrathin sections (600 A) with a Phillips transmission electron microscope.

Statistical Analysis

Data are expressed as mean ± standard error of the mean. Results are compared by analysis of variance and by Student's t test. A p value of less than 0.05 was accepted as significant.

Results

Circulation of the Rat Lung

Injection of disulfine blue dye into the rat lungs indicated that the pulmonary circulation provided the majority of blood flow to the rat lung (Table 1). Group 1 animals (shams) showed a rapid color change in both lungs. In groups 2 and 3, in which the vessels and bronchus were clamped with or without stripping the hilum, no color change was seen, indicating that essentially all blood flow to the lung comes from the hilum. In groups 4 and 5, the bronchus was not clamped; when the bronchus was stripped (group 4), all flow to the lung was eliminated, whereas when no stripping was performed (group 5), a delayed and minimal color change was seen, indicating a minor amount of flow. These results indicate that the pulmonary circulation provides the overwhelming amount of blood supply to the rat lung and that stripping the hilum eliminates the small contribution of bronchial circulation.

Ischemia-Reperfusion Injury

ALBUMIN LEAK. At each time point used, the lung parenchymal leak index was calculated for the ischemic left lung, the contralateral nonischemic right lung, and the sham-operated left and right lungs (Table 2). For ischemic times of 60 minutes or more, the leak index in the ischemic lung was significantly greater ($p < 0.05$) than in either the contralateral control lung or in either lung of the sham-operated animals. Also, the leak index increased in the ischemic lungs as the ischemic interval was prolonged. There was no significant difference in injury between the internal control lung or the sham-operated lungs (Fig 2). These results indicate that warm ischemia of the lung for 60 minutes or more caused significant damage, which was progressive over time.

HISTOLOGIC EVALUATION. Light microscopy was performed on lungs that underwent 90 and 180 minutes of ischemia and reperfusion (Fig 3). For the 90-minute lungs, 20 fields per lung were analyzed for the number of intraalveolar erythrocytes (ie, number of alveoli containing red blood cells/HPF) and for the number of neutrophils seen per HPF. Results in Table 3 show that the ischemic lungs had more red blood cell–containing alveoli per HPF than the contralateral right lungs or the shams. Also there was no histologic evidence of neutrophil infiltration into the ischemic lungs.

Electron microscopy on the same lungs showed that the ischemic lungs had evidence of damage demonstrated by endothelial cell blebbing (Fig 4).

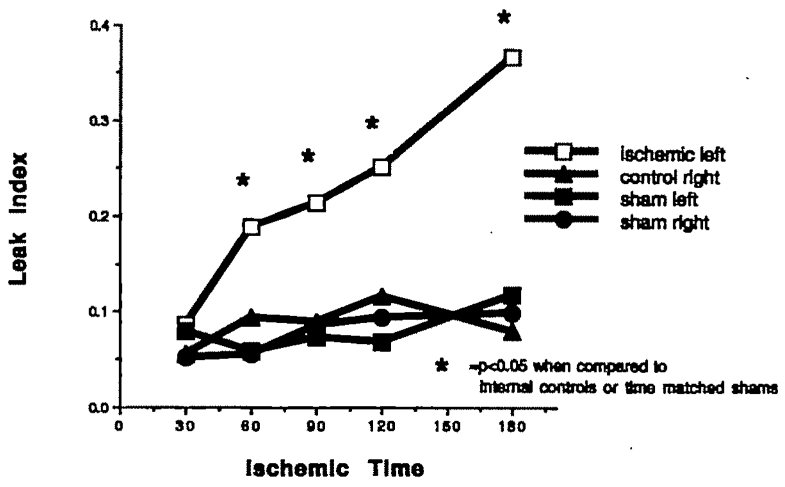

Fig 2. Differences in the mean leak indices between the ischemic lungs, contralateral control lungs, and sham lungs at the varying ischemic times.

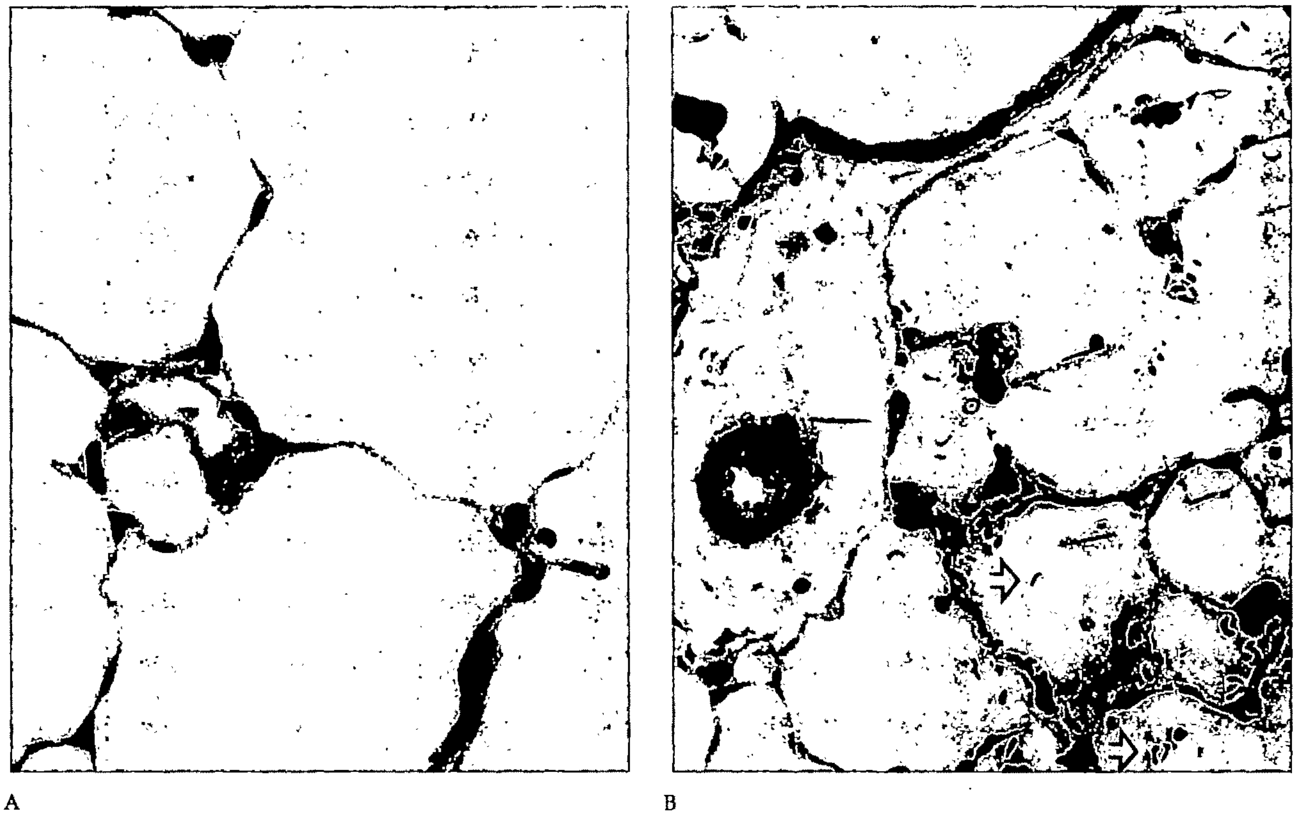

Fig 3. Light microscopy: (A) Sham lung after 210 minutes of continuous ventilation and perfusion (hematoxylin and eosin, ×140 before 25% reduction). (B) Lung after 180 minutes of ischemia followed by 30 minutes of reperfusion; note the intraalveolar red blood cell infiltration (open arrows) *(hematoxylin and eosin, ×100 before 25% reduction).*

Neutrophils and Ischemia-Reperfusion Lung Injury

NEUTROPHIL DEPLETION. In the antibody-treated group (PMN depleted, n = 16) the average number of PMNs before antibody therapy was 2,958 ± 389; it was 44 ± 17 24 hours after antibody treatment. The difference in PMN count was significant ($p < 0.0001$). In the group treated with serum without antibody (nondepleted group), the average number of PMNs was 2,233 ± 230 before therapy and 2,031 ± 211 24 hours after treatment. There was no statistical significance in the PMN count after treatment. Therefore, the antibody therapy did significantly abolish the PMN count to 1.5% of the pretreatment value.

Table 3. Histologic Evaluation of Ischemic and Sham Animals After 90 Minutes of Ischemia/Reperfusion[a]

Group	Alveoli/Field Containing RBCs	PMNs/HPF	N
Ischemic left	$11.2 \pm 0.9^{b,c}$	1.3 ± 0.2	2
Control right	1.9 ± 0.3	1.3 ± 0.2	2
Sham left	2.3 ± 0.3	1.5 ± 0.2	2
Sham right	1.6 ± 0.3	1.4 ± 0.2	2

[a] All results are expressed as mean ± standard error of the mean for 20 high-power fields. [b] $p < 0.05$ compared with sham animals. [c] $p < 0.05$ compared with internal controls.

HPF = high-power field; PMN = leukocyte; RBC = red blood cell.

ALBUMIN LEAK. Albumin leak was determined in both PMN-depleted and nondepleted lungs after 90 and 180 minutes of ischemia. The results, displayed in Table 4, showed in both the depleted and nondepleted groups that ischemia produced a significantly greater albumin leak index in the left lungs versus the contralateral nonischemic right lungs, and no significant difference in the amount of I-R injury was seen in the experimental left lungs at both 90 and 180 minutes whether or not PMNs had been depleted. Thus, there was no indication that neutrophil depletion will attenuate I-R injury.

Comment

The lung is a unique organ that has two sources of oxygen, vascular and alveolar. In addition, there are two vascular supplies to the lung, the pulmonary blood supply with low oxygen tension and the bronchial vessels with high oxygen tension. Fisher and associates [8] demonstrated intact lung cellular metabolism at low oxygen tensions, with decreases in adenosine triphosphate (ATP) content and ATP/adenosine diphosphate ratios only after the alveolar oxygen tension was reduced to 0.7 mm Hg. Because the lung has relatively low oxygen requirements compared with total body oxygen consumption [9] and lung cell oxygen requirements do not fluctuate with activity, the pulmonary vasculature alone is more than adequate to maintain pulmonary parenchymal viability.

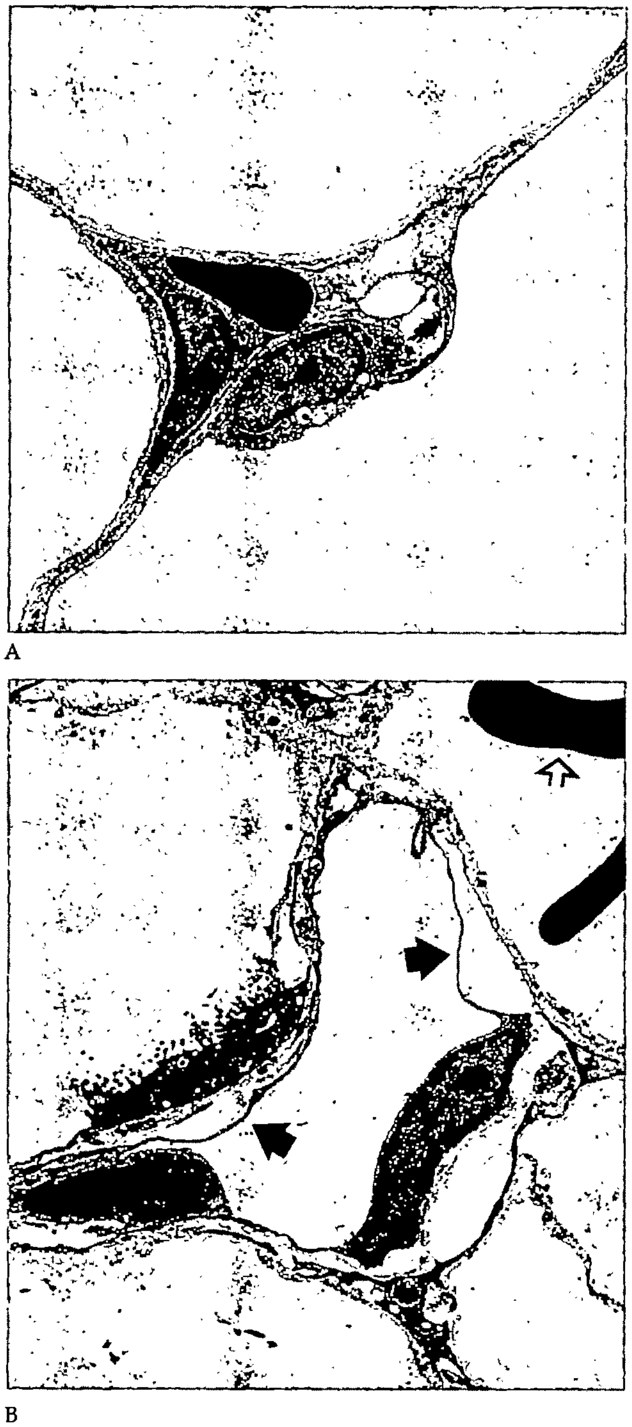

Fig 4. Electron microscopy: (A) Sham lung after 210 minutes of continuous ventilation and perfusion (×6,400 before 28% reduction). (B) Lung after 180 minutes of ischemia followed by 30 minutes of continuous ventilation and perfusion; note intraalveolar red blood cell infiltration (open arrows) *and endothelial cell blebbing* (closed arrows) *(×10,600 before 28% reduction).*

Table 4. Leak Index in Leukocyte-Depleted and Nondepleted Animals

Ischemic Time (min)	Group	Leak Index		N
		PMN-Depleted	Nondepleted	
90	Ischemic left lung	0.208 ± 0.033[a,b]	0.222 ± 0.063	8
	Control right lung	0.050 ± 0.014	0.063 ± 0.015	8
180	Ischemic left lung	0.218 ± 0.040[a,b]	0.241 ± 0.038	8
	Control right lung	0.100 ± 0.028	0.101 ± 0.032	8

[a] $p < 0.05$ when compared with internal controls. [b] No significant difference when compared with time-matched ischemic lungs in the nondepleted group.

This efficient use of oxygen may be related to the short diffusion distances in the lung and to the fact that ventilated alveolar spaces provide a large gas reservoir at relatively constant oxygen tension. The lung therefore avoids the uncertainty of cellular oxygen tension as a function of vascular oxygen delivery. Thus, it appears that either ventilation or perfusion alone is sufficient to maintain lung parenchymal viability [10].

Because of the dual oxygen supply, pulmonary ischemia was not considered important. However heart/lung and lung transplantation made I-R injury clinically important and a limiting factor for these procedures. Methods of avoiding I-R injury in remote lung harvests have included hypothermic flushing [13, 14], autoperfusion [15, 16], and core-cooling using cardiopulmonary bypass with stagnant hypothermic storage of the organs for transport [17].

Our laboratory results coincided with the work of others described above with consideration to hypothermia, attenuation of I-R injury with continuous ventilation, and the role of oxygen free radicals in the formation of I-R lung injury [3, 4, 18]. However, our findings as to the role of circulating blood elements, in particular, neutrophils, differed quite markedly from those of Hall and co-workers [5] and Pillai and colleagues [6], who reported on the benefit of leukocyte depletion from blood reperfusate in ischemic lungs. Because the difference could be explained by the marked variations between our ex vivo model and their in vivo models, this present study was undertaken.

Because our previous work was accomplished with an ex vivo model, there were several steps necessary to confirm the reliability and reproducibility of an intact live (in vivo) animal model. First, it was important to determine the role of pulmonary and bronchial circulation in the rat lung to ensure that perfusion could be completely blocked for the desired ischemic intervals. Disulfine blue dye technique was used for this purpose. By dividing the inferior pulmonary ligament and stripping all hilar supportive tissues from the pulmonary artery, vein, and bronchus we were able to completely block blood flow when the pulmonary blood vessels were selectively clamped. This total blockage of blood flow to the lung was irrespective of whether the bronchus was clamped. Animals in which we divided the ligament but kept the hilar supportive tissues intact while selectively clamping the pulmonary vessels and bronchus had delayed color change indicating low perfusion to the lung persisted through the bronchial circulation within the supportive tissues of the hilum. Therefore, to accomplish total occlusion of blood flow to our experimental lungs we divided the inferior pulmonary ligament and stripped all supporting tissue from the hilum before selective clamping of the hilar structures.

To establish the reliability and reproducibility of the ^{125}I-BSA leak index for quantification of I-R injury in the intact rat lung model, we studied several groups of animals at varying ischemic times and correlated the leak indices. Warm ischemia caused progressive ^{125}I-BSA leak over time with the values reaching significance ($p < 0.05$) after 60 minutes. For the 90-minute time interval there was a positive correlation between the ^{125}I-BSA leak index and the histologic and electron microscopic findings, supporting ^{125}I-BSA as a reliable and reproducible method to quantitate I-R lung injury in the intact rat lung model.

The role of neutrophils in the development of early significant I-R injury in the intact rat model was addressed by comparing leak indices between neutrophil-depleted versus nondepleted rats. Both groups of animals had significant injury in the experimental lungs versus the internal contralateral controls at both 90 and 180 minutes of ischemia; furthermore, there was no significant difference when comparing the leak indices between the injured lungs in both the depleted and nondepleted animals. This supports our previous findings, using the ex vivo rat lung model [4], that neutrophils are not necessary for I-R injury.

The response to I-R injury is multifaceted and both organ and species specific. Fantone [19] breaks down I-R injury into three components: parenchymal cell, vascular tissue, and inflammatory cell response. The dynamic interaction of these components in relationship to the duration of ischemia as well as the reperfusion time studied may well account for the differences in results in our studies versus those of others.

At the cellular level, ischemia initiates a shift from aerobic to anaerobic metabolism with a decrease in the levels of cellular ATP, accumulation of lactic acid, and decrease in tissue pH. The decrease in cellular ATP levels results in dysfunction of ATP-dependent enzymes causing altered cellular function. Cellular membrane ion transport is affected with resultant depolarization and accumulation of calcium and fluid within the cells. The cells subsequently swell, and calcium-sensitive enzymes such as phospholipases are activated with degradation of membrane phospholipids and the formation of blebs [20] as seen by electron microscopy in this study.

Reperfusion of specific parenchymal cells and tissues has been shown to have deleterious effects [21] secondary to the formation of reactive metabolites of molecular oxygen, including superoxide anion, hydrogen peroxide, hydroxyl radical, and other free radical species and oxidants. Two parenchymal cellular sources of reactive oxygen species are xanthine dehydrogenase/oxidase and mitochondrial electron transport enzyme systems. The mechanism of xanthine dehydrogenase/oxidase during ischemia is based on accumulation of intracellular calcium and the irreversible conversion of xanthine dehydrogenase to xanthine oxidase. Adenosine triphosphate is broken down during ischemia to purine nucleotide-degradation products, including hypoxanthine. Xanthine oxidase converts hypoxanthine to xanthine using molecular oxygen as its terminal electron acceptor, and toxic oxygen metabolites in the form of superoxide anion and hydrogen peroxide are generated. Our laboratory previously studied the role of xanthine oxidase in the formation of I-R lung injury using an ex vivo rat lung model [18]. Lungs were rendered ischemic by interrupting ventilation and perfusion for 2 hours at 37°C. The lungs were reperfused with whole blood with or without lodoxamide (xanthine oxidase inhibitor), and injury was determined by the accumulation of ^{125}I-BSA in lung parenchymal and alveolar lavage fluid. Lung effluent was collected immediately before and after ischemia for analysis of uric acid, the end product of xanthine oxidase activity. Lodoxamide significantly reduced lung injury, and decreased uric acid levels in the lung effluent confirmed inhibition of xanthine oxidase. These studies confirmed the role of parenchymal cellular activity in the formation of I-R lung injury via toxic oxygen metabolites.

Phospholipase activation by cellular calcium accumulation causes cellular membrane breakdown with release of arachidonic acid. Once released, arachidonic acid is metabolized by several enzymatic pathways. The formation of arachidonic acid metabolites derived from the cyclooxygenase pathway has been associated with I-R injury of multiple organs [22–24]. Our laboratory demonstrated the association of arachidonic acid breakdown products via the cyclooxygenase pathway with I-R lung injury [25]. Using the ex vivo rat model, lungs subjected to I-R injury showed significant ^{125}I-BSA leaks in conjunction with increased levels of 6-keto-prostaglandin $F_{1\alpha}$ (a stable metabolite of arachidonic acid metabolism via the cyclooxygenase pathway) in comparison with nonischemic controls. Indomethacin and flubiprofen cyclooxygenase inhibitors significantly reduced lung injury and the formation of 6-keto-prostaglandin $F_{1\alpha}$. These studies also support the role of parenchymal cells in the development of I-R lung injury.

Vascular tissue contributes to I-R lung injury secondary to endothelial swelling and capillary narrowing during reperfusion with subsequent extension of low flow and tissue ischemia. The narrowing of capillaries and plugging by granulocytes has been implicated as the underlying mechanism of the no-reflow phenomenon [26]. In addition, endothelial cell damage may alter secretion of specific mediators. Decreased production of prostaglandin I_2, a potent vasodilator, by the endothelial cells could potentially decrease tissue perfusion while enhanced synthesis of endothelial cell-derived procoagulant activity would function to promote thrombosis and augment injury.

Both damaged parenchymal cells and endothelial cells release mediators that can activate the complement and coagulation systems, resulting in the release of potent soluble mediators that promote the recruitment and activation of the third component of injury, the inflammatory response. Platelet, leukocyte, and monocyte aggregation compromises blood flow and further inhibits oxygenation of tissue. Furthermore, secretory products of these inflammatory cells have physiologic effects on both endothelial and parenchymal cells. Platelet secretion of thromboxane A_2 and serotonin promotes smooth muscle cell contraction and vascular narrowing. The local release of proteases and the generation of toxic oxygen metabolites by activated neutrophils and monocytes enhances endothelial cell and parenchymal cell injury with the degradation of tissue structural components [21, 27]. In addition, the release of platelet-activating factor by neutrophils and cytokines such as tumor necrosis factor by monocytes further amplifies the inflammatory response and accentuates ischemic injury [28, 29].

In this particular study, neutrophils were unnecessary for the development of significant injury as noted by the accumulation of ^{125}I-BSA in the ischemic groups for both the neutrophil-depleted and nondepleted rats when compared with contralateral nonischemic controls. In addition, there was no significant difference in the amount of injury in the ischemic lungs of the depleted and nondepleted groups. Furthermore, there was no accumulation of neutrophils in the damaged lungs of the nondepleted rats when compared with the injured lungs of the depleted rats as noted by both histologic and electron microscopic survey.

We can postulate that in this model the inflammatory response, using neutrophils, was not present secondary to the short reperfusion interval before injury analysis. Longer reperfusion times may be associated with increased injury in the nondepleted group in association with accumulation of leukocytes in lung parenchyma. Because the short reperfusion times in these experiments parallel those used in the ex vivo model, it is quite possible the same parenchymal cell mechanisms of injury that were active in the ex vivo model are also present in this in vivo model. However, one could postulate that the possible mechanism of damage in the depleted groups, treated with antibody or control serum, might be secondary to complement activation from the injected antisera and not due to I-R injury. This seems highly unlikely as complement activation causes neutrophil sequestration, which was not histologically present in this study; in addition, the animals that underwent I-R injury to validate the in vivo model did not receive antisera, and they showed significant injury without neutrophil infiltration.

In conclusion, I-R injury of the lung is a complex mechanism that comprises many components. We are not saying that the inflammatory component with neutrophil infiltration and activation is not an important part of I-R injury of the lung but that it is not necessary for the development of significant injury. The parenchymal and vascular components also appear to make an important contribution to the development of I-R injury. The interaction of these components will define the extent of injury, and all components are not necessary for significant injury to occur. The differences in response to a particular I-R insult may be species and time dependent.

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DISCUSSION

DR WATTS R. WEBB (New Orleans, LA): First I would like to congratulate you for a very beautiful model and a beautiful study, well presented. Some years ago we did work in dogs using an antiplatelet serum that produced a profound thrombocytopenia, reducing their platelet count down to almost zero. In using three models, the ischemic model, the endotoxin model, and even the oleic acid model, we were able to demonstrate that if the platelets were reduced to almost zero, we could tremendously ameliorate the lung injury that was performed, suggesting that platelets are probably essential or at least play a great role in the lung injury that occurs. That was a different model; it was a dog instead of a rat. Have you looked at the role of platelets in your particular model?

DR STEIMLE: No, we have not analyzed the role of platelets in this particular model, and in fact we took pains to ensure that the antibody we used did not reduce the number of platelets available. That is certainly another area of investigation to open.

DR JOEL D. COOPER (St. Louis, MO): So you did in fact monitor platelet count and did not find it depressed.

DR STEIMLE: That is correct. The antibody was specific to neutrophils and did not reduce platelet counts.

DR HANI SHENNIB (Montreal, Que, Canada): This is a very nice study. Dr Webb asked my first question. The few questions I have are, first, are there antiplatelet antibodies that can be used in a similar study in the rat? Second, were these animals heparinized before clamping of the hilum? Third, just being a devil's advocate, the antibody reduced the neutrophil count to less than 250/μL. Maybe you only need 100 neutrophils per microliter to release mediators that can cause ischemic reperfusion injury.

DR STEIMLE: I will answer your questions in order. First, we have not tried to create an antiplatelet antibody, but there are other investigators at the University of Michigan who have investigated ischemia-reperfusion injury in other organs, and I believe they do have an antiplatelet antibody available, although we have not attempted to use this antibody ourselves. To answer your second question, no, we deliberately did not heparinize the animals because of the question of heparin effect, especially on platelet function, in ischemia-reperfusion injury. In answer to your third question, most of our animals did have total neutrophil counts that were actually much less than 250/μl, but there is always the question of whether even a very, very small number of neutrophils could produce a significant amount of injury. Of course it is almost impossible to confirm that we had complete removal of all neutrophils. So the question remains open.

DR TIMOTHY S. HALL (Baltimore, MD): When assessing lung reperfusion injury, I think warm ischemia represents a different entity than that induced with cold preservation, particularly in the rat. I would propose that our results with leukocyte depletion, because they focused on cold ischemia, demonstrated a different result. We found that white blood cell depleting with filtering techniques was very effective at limiting reperfusion injury. But there is still ongoing injury within the tissue. Recent experience with reperfusion involving other injury mechanisms, such as endothelial cell-derived sources of free radicals, has shown that white blood cells do have an active part in reperfusion injury once they are activated. They represent an amplifying mechanism that can be quite dangerous. We went to filtering white blood cells because the lung is such a harborer of leukocytes, and so many of them are demarginated at a time of stress, particularly during operation. It is hard to quantitate exactly what the counts are. Many of the leukocyte-depleting agents, even antibodies, lead to lung injury and represent a difficult covariable to exclude from the scientific design. The question of how low a white blood cell count you need to avoid that injury is unknown. We were able to deplete down to less than 100/μl in our studies and showed pretty reproducible suppression of injury in cold ischemic models.

My question to you is about your white blood cell counts. Did you have the opportunity to measure if there was a surge of white blood cells, either from demargination or from the lungs themselves?

DR COOPER: You mean in the depleted animals, whether there were sequestered neutrophils that were then released?

DR HALL: Exactly. Did you confirm in the depleted animals that they truly were white blood cell depleted? The other issue you might address is what other mechanisms of reperfusion injury are at work. The rat represents an excellent model to study reperfusion injury because it does have serum levels of xanthine oxidase, which can produce the lung injury without white blood cell involvement, particularly with warm ischemia.

DR STEIMLE: There are a number of different issues to address. The first comment I would make is that certainly one of the difficulties in evaluating ischemia-reperfusion injury models is that many of the findings could well be species specific. We used a rat lung model for a number of reasons, partially having to do with the advantages of using rats for lung transplantation and therefore having pure syngenic lines to work with. Certainly the use of rats as compared with dogs, sheep, or rabbits, which are the other commonly used species, could affect the role of the neutrophil during ischemia-reperfusion injury of the lung. I think it is clear that neutrophils do play a role, and the exact role probably is species specific.

To quantify whether neutrophils were sequestered in the lung during our experiments, we used both a myeloperoxidase assay and histologic analysis. Both techniques showed that there was no sequestration of neutrophils within the lung.

Certainly there are other important mechanisms of ischemia-reperfusion injury besides the neutrophil-mediated inflammatory response. The other two major mechanisms are the parenchymal cellular mechanism, which uses both the xanthine oxidase and the cyclooxygenase pathways, as well as the vascular tissue mechanism, with release of vasodilators and the no-reflow phenomenon. I believe it is the interaction of these three components, as well as other more minor mechanisms that have not been investigated to date, that causes ischemia-reperfusion injury.

Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1994 may begin the recertification process in 1992. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1992. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

University of Wisconsin Versus Modified Euro-Collins Solution for Lung Preservation

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In a canine model, the quality of lung preservation was assessed using pulmonary artery flush after prostacyclin administration with either modified Euro-Collins solution or University of Wisconsin solution. Twelve combined heterotopic heart and orthotopic left lung allotransplantations were performed after 6 hours of cold ischemia. Myocardial preservation was achieved using St. Thomas Hospital solution. Donor organs were anastomosed parallel to the recipient's heart and right lung, and the superior vena cava inflow was directed into the transplanted heart–left lung block after ligation of the recipient's superior vena cava proximal to the caval anastomosis. Postoperatively, cardiorespiratory function was evaluated separately for donor and recipient organs at an inspired oxygen fraction of 0.4 for a maximum of 12 hours. Significantly improved oxygenation and lower pulmonary vascular resistance index of the donor lung was observed in the University of Wisconsin + prostacyclin group, whereas pulmonary artery pressures showed no significant differences in between both groups. It is concluded that superior results in lung preservation can be achieved with pulmonary artery flush perfusion using University of Wisconsin solution and prostacyclin when compared with Euro-Collins solution and prostacyclin.

(Ann Thorac Surg 1992;53:74–9)

The clinical introduction of lung and heart-lung transplantation has offered new therapeutical options for the increasing number of patients with end-stage pulmonary and cardiopulmonary diseases [1–5]. Particularly owing to the scarcity of donor organs and the problems encountered with donor transfer to the recipient's hospital, several methods for distant organ procurement have been developed in the past [2, 6–8]. Currently, pulmonary artery flush perfusion with Euro-Collins solution (ECS) in combination with prostacyclin (PGI_2) is most frequently used for lung preservation [9–12]. Acceptable results can be achieved clinically with ischemic times up to 4 hours [13]. Because the University of Wisconsin solution (UWS) has already been established successfully in kidney and liver transplantation [14, 15], we evaluated the applicability and quality of UWS for lung preservation after pretreatment with PGI_2 in comparison with our current clinical standard as represented by ECS + PGI_2 [9, 16].

Material and Methods

Twelve mongrel dogs (mean weight, 18.7 ± 5.3 kg) served as organ donors. After intramuscular administration of methylparaben (0.5 mL/kg) (Bayer AG, Leverkusen, Germany) and levomethadon (0.3 mL/kg) (Hoechst AG, Frankfurt, Germany) and intravenous injection of sodium pentobarbital (0.05 mL/kg) (Rhone Merieux GmbH, Laupheim, Germany), orotracheal intubation was performed. The dogs were paralyzed with pancuronium bromide (4 mg initial dose) (Organon AG, Oberschleißheim, Germany) and ventilated with 40% oxygen and 60% nitrous oxide using a tidal volume of 15 mL/kg, a respiratory rate of 12 breaths/min, and a positive end-expiratory pressure of 5 cm H_2O. General anesthesia was maintained by repeated intravenous application of fentanyl (0.1 mg/h) (Janssen GmbH, Neuss, Germany) in combination with etomidate (4 mg/hour) (Janssen GmbH), and pancuronium bromide (2 mg/h) was used for relaxation. An arterial line was placed in the left carotid artery and a thermodilution catheter was inserted in the pulmonary artery through the left internal jugular vein in all animals.

The operative technique for donor and recipient operations was described previously by Wahlers and associates [9]. The donor animals were divided into two groups according to the method of pulmonary preservation: in group 1 (n = 6) pulmonary artery flush perfusion was performed with modified ECS (60 mL/kg), whereas in group 2 (n = 6) UWS (60 mL/kg) was used. The solution compositions were as follows:

Euro-Collins solution	
K_2HPO_4	2.05 g/L
KH_2PO_4	7.40 g/L
KCl	1.12 g/L
$NaHCO_3$	0.84 g/L
$MgSO_4$	1.00 g/L
Glucose	6.50 g/L

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University of Wisconsin solution

Hydroxyethyl starch	50.00 g/L
Lactobionic acid	35.83 g/L
K_2HPO_4	3.40 g/L
$MgSO_4$	1.23 g/L
Raffinose	17.83 g/L
Adenosine	1.34 g/L
Allopurinol	0.14 g/L
Glutathione	0.92 g/L
Insulin	40 U/L
Dexamethasone	16 mg/L
Penicillin G	200,000 U/L

Euro-Collins solution perfusion was performed by gravity. Owing to the higher viscosity of UWS a roller pump was used for perfusion in group 2. Prostacyclin (Wellcome, Großburgwedel, Germany) was given intravenously over a 10-minute period (20 ng · kg^{-1} · min^{-1}) immediately before aortic cross-clamping. Care was taken to achieve perfusion pressures according to the previously obtained individual pulmonary artery pressures. For cardioplegia St. Thomas Hospital solution (20 mL/kg, 4°C) was used in all donors. The organ block was immersed in cold ECS or UWS without further dissection and stored at 4°C for about 5 hours.

The anesthetized recipient animals (mean weight, 27.6 ± 4.9 kg) were prepared during the organ storage period as described above. Briefly, a left pneumonectomy was performed. Before the implantation, the right lung was removed from the heart-lung block and the donor heart with the adjacent left lung was transplanted as described earlier [9, 16]. Anastomoses were performed end-to-side between the donor's and recipient's superior venae cavae, and the donor's descending aorta was sutured end-to-side to the proximal part of the recipient's descending aorta. Ligation of the recipient's superior vena cava proximal to the anastomosis after 30 minutes of reperfusion provided a separation of the donor and recipient pulmonary circulation (Fig 1). The donor trachea was intubated with an endotracheal tube inserted through the second intercostal space and ventilated separately (oxygen 40%/nitrous oxide 60%; tidal volume, 10 mL/kg; respiratory rate, 12/min; positive end-expiratory pressure, 5 cm H_2O). The chest was closed temporarily.

A pulmonary artery thermodilution catheter was placed through the left internal jugular vein and the donor's heart into the transplanted lung. An additional thermodilution catheter was inserted through the right femoral vein and the recipient's heart into the right pulmonary artery. This allowed measurement of cardiac output and pulmonary artery pressure in both circulations. Additional venous lines were placed in both left atria. Heart rate, arterial pressure, central venous pressure, pulmonary artery pressure (PAP), left atrial pressure (LAP), cardiac output, and left atrial blood gas analyses were obtained every hour until the postoperative course was terminated or the animal died. Calculation of cardiac index (CI) and pulmonary vascular resistance index (PVRI) were performed according to standard formulas.

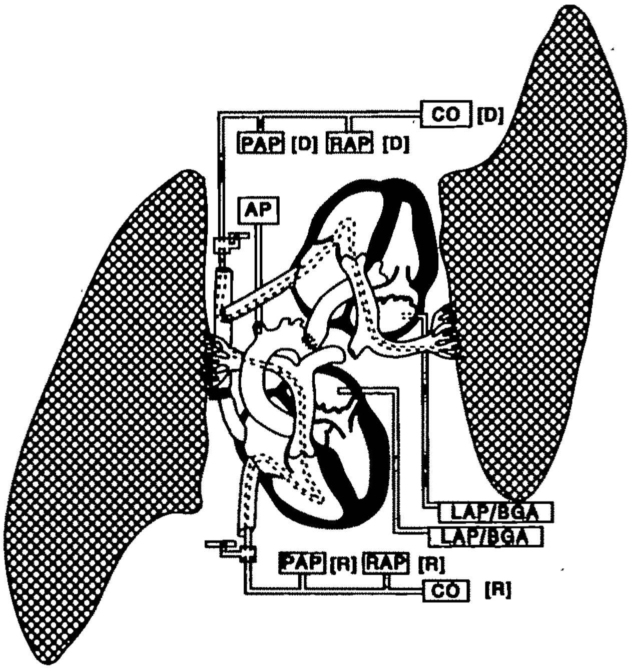

Fig 1. Heterotopic heart and orthotopic left lung transplantation. (AP = *arterial pressure;* BGA = *left atrial blood gas analysis;* CO = *cardiac output;* D = *donor;* LAP = *left atrial pressure;* PAP = *pulmonary artery pressure;* R = *recipient;* RAP = *right atrial pressure.)*

Data were expressed as mean values ± standard deviation. To exclude influences of baseline data on postoperative results, correlation analysis was performed using an analysis of covariance. Values of P less than 0.05 were considered significant.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Donor hemodynamic data showed no significant differences for PAP, CI and PVRI. In group 2, LAP was significantly lower (group 1, 9.0 ± 3.4 mm Hg; group 2, 5.0 ± 2.0 mm Hg; $p < 0.05$) and the arterial oxygen tension (pO_2) was slightly elevated (group 1, 190.3 ± 10.2 mm Hg; group 2, 222.6 ± 22.8 mm Hg; $p < 0.01$) (Table 1). During harvesting, perfusion pressures did not exceed the native mean PAPs (group 1: perfusion pressure, 13.5 ± 3.5 mm Hg; PAP, 15.7 ± 4.8 mm Hg; group 2: perfusion pressure, 10.0 ± 5.8 mm Hg; PAP, 14.3 ± 2.4 mm Hg); there were no significant variations in perfusion pressure and donor PAP values between group 1 and group 2. The temperature of the perfusion solution (group 1, 4.2° ± 0.3°C; group 2, 4.0° ± 0.6°C), the perfusion time (group 1, 233 ± 46 seconds; group 2, 211 ± 34 seconds), the organ temperature after perfusion (group 1, 9.3° ± 2.7°C; group 2, 11.0° ± 3.9°C), and the total ischemia time of the donor organs (group 1, 368.3 ± 30.4 minutes; group 2, 362.8 ±

Table 1. Donor Hemodynamic and Oxygenation Data[a]

Variable	ECS + PGI_2	UWS + PGI_2
PAP (mm Hg)	15.7 ± 4.8	14.3 ± 2.4[b]
LAP (mm Hg)	9.0 ± 3.4	5.0 ± 2.0[c]
CI ($L \cdot min^{-1} \cdot m^{-2}$)	3.89 ± 1.07	3.25 ± 1.43[b]
PVRI ($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	197 ± 29	199 ± 100[b]
pO_2 (mm Hg)	190 ± 10	223 ± 23[d]

[a] Data are shown as mean ± standard deviation. [b] P = not significant. [c] $P < 0.05$. [d] $P < 0.01$.

CI = cardiac index; ECS = Euro-Collins solution; LAP = left atrial pressure; PAP = pulmonary artery pressure; PGI_2 = prostacyclin; pO_2 = arterial oxygen tension; PVRI = pulmonary vascular resistance index; UWS = University of Wisconsin solution.

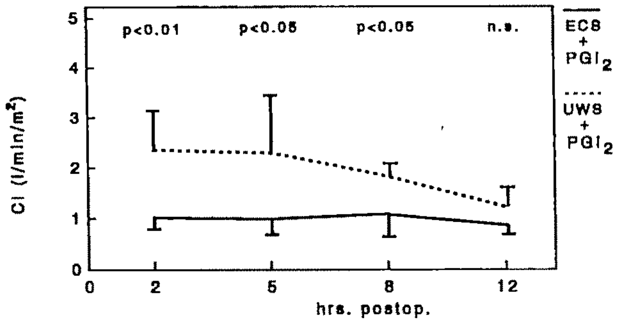

Fig 3. Postoperative donor cardiac index (CI) (mean ± standard deviation). (ECS = Euro-Collins solution; n.s. *= not significant;* PGI_2 *= prostacyclin; UWS = University of Wisconsin solution.)*

27.3 minutes) also showed no significant differences. The central venous pressure was adjusted in both venous systems at approximately 6 to 8 mm Hg during the entire postoperative course in both groups.

In both groups no recipient animal died during the first 8 postoperative hours. Two dogs of each group died between 8 and 12 hours postoperatively. Causes of premature deaths of the animals were progressive cardiac failure with low output and dysrhythmias in all cases.

Improved oxygenation of the donor lung after transplantation was observed in the UWS + PGI_2 group compared with the ECS + PGI_2 group throughout the entire postoperative period (Fig 2). During the first 5 postoperative hours pO_2 values were elevated in group 2 compared with group 1, but the differences were not significant. All pO_2 values obtained between 6 and 12 hours postoperatively showed a significant improvement in the UWS + PGI_2 group. In group 1 mean values of left atrial pO_2 decreased significantly during the postoperative course from 190 ± 56 mm Hg at 2 hours to 123 ± 34 mm Hg at 12 hours ($p < 0.05$) whereas the pO_2 values in group 2 were stable after transplantation (2 hours, 235 ± 106 mm Hg; 12 hours, 215 ± 47 mm Hg; not significant).

Cardiac index was elevated in group 2 compared with group 1, and this difference was significant during the first 8 hours postoperatively (CI at 2 hours: group 1, 1.06 ± 0.29 $L \cdot min^{-1} \cdot m^{-2}$; group 2, 2.34 ± 0.8 $L \cdot min^{-1} \cdot m^{-2}$; $p < 0.01$; at 5 hours: group 1, 1.04 ± 0.43 $L \cdot min^{-1} \cdot m^{-2}$; group 2, 2.28 ± 1.16 $L \cdot min^{-1} \cdot m^{-2}$; $p < 0.05$; and at 8 hours: group 1, 1.15 ± 0.62 $L \cdot min^{-1} \cdot m^{-2}$; group 2, 1.83 ± 0.21 $L \cdot min^{-1} \cdot m^{-2}$; $p < 0.05$). Although CI was stable in both groups during this time, in the later postoperative course CI decreased in group 2 ($p < 0.05$). Despite this decrease, the CI values in group 2 were still elevated compared with those in group 1, but the differences were not significant (CI at 12 hours: group 1, 1.05 ± 0.23 $L \cdot min^{-1} \cdot m^{-2}$; group 2, 1.22 ± 0.18 $L \cdot min^{-1} \cdot m^{-2}$, not significant) (Fig 3).

Mean PAP ranged postoperatively between 14.2 ± 7.3 mm Hg at 2 hours and 18.3 ± 6.7 mm Hg at 12 hours in group 1 and between 8.6 ± 2.5 mm Hg at 2 hours and 11.5 ± 4.7 mm Hg at 12 hours in group 2 (Fig 4). In both groups a slight, but not significant increase in PAP was found throughout the postoperative period. Comparing the corresponding postoperative PAP values of both groups, no significant differences were found at any time.

Mean values of LAP of the donor hearts after transplantation ranged between 6.8 ± 4.0 mm Hg at 2 hours and 8.3 ± 3.9 mm Hg at 12 hours in group 1 compared with 4.0 ± 1.8 mm Hg at 2 hours and 6.8 ± 3.9 mm Hg at 12 hours in

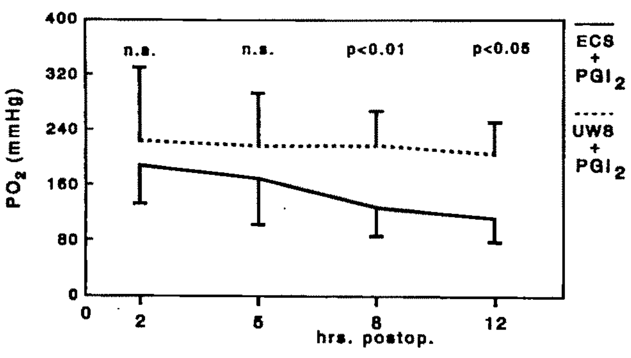

Fig 2. Postoperative donor left atrial oxygen tension (PO_2) *values (mean ± standard deviation). (ECS = Euro-Collins solution;* n.s. *= not significant;* PGI_2 *= prostacyclin; UWS = University of Wisconsin solution.)*

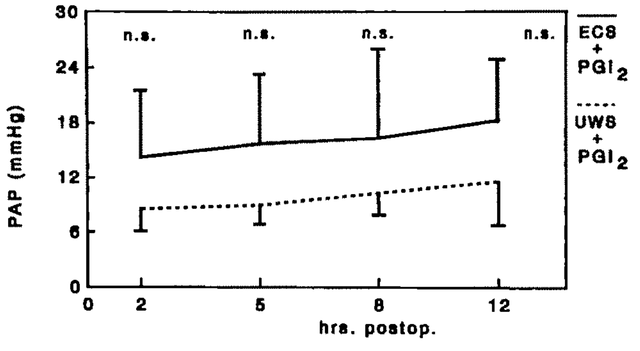

Fig 4. Postoperative donor mean pulmonary artery pressure (PAP) (mean ± standard deviation). (ECS = Euro-Collins solution; n.s. *= not significant;* PGI_2 *= prostacyclin; UWS = University of Wisconsin solution.)*

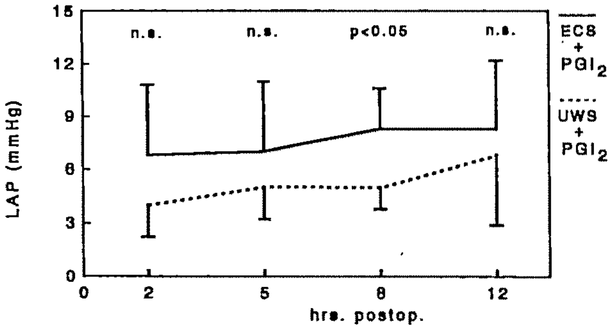

Fig 5. Postoperative donor left atrial pressure (LAP) (mean ± standard deviation). (ECS = Euro-Collins solution; n.s. *= not significant;* PGI$_2$ *= prostacyclin; UWS = University of Wisconsin solution.)*

group 2 (Fig 5). In both groups a slight but not significant increase of LAP was measured. Analysis of corresponding LAP values of both groups during the postoperative course revealed a statistically significant difference only at 8 hours postoperatively (LAP at 8 hours: group 1, 8.8 ± 2.3 mm Hg; group 2, 5.3 ± 1.2 mm Hg; $p < 0.05$).

Calculated PVRI was elevated postoperatively in both groups and ranged between 705 ± 313 dyn · s · cm^{-5} · m^2 at 2 hours and 947 ± 732 dyn · s · cm^{-5} · m^2 at 12 hours in group 1 and between 196 ± 132 dyn · s · cm^{-5} · m^2 at 2 hours and 394 ± 40 dyn · s · cm^{-5} · m^2 at 12 hours in group 2 (Fig 6). In both groups a significant increase in PVRI was noted during the postoperative course ($p < 0.05$). Pulmonary vascular resistance index values of group 1 were elevated at all times postoperatively compared with the corresponding values of group 2. These differences reached statistical significance at 2, 5, and 8 hours postoperatively.

Between the two groups no significant differences were found in recipient data during the postoperative course comparing corresponding values of CI, PAP, LAP, and PVRI; there was a significant decrease in pO$_2$ values in both groups ($p < 0.05$).

Comment

First attempts at clinical lung transplantation failed early owing to problems caused by inadequate methods for lung preservation, aside from infectious complications and rejections [17]. As a consequence, different methods and techniques for lung procurement were investigated to improve preservation quality in clinical transplantation.

Initially the lungs were harvested on-site and transplanted immediately without any attempts at preservation [17]. The limited donor availability for on-site organ procurement encouraged further development of different techniques for perfusion and preservation allowing distant organ procurement and longer ischemic times. Donor core cooling by extracorporeal circulation [8, 18] and single-flush perfusion of the pulmonary artery using either modified Euro-Collins solution [2, 9–13] or cold blood [7] have been established. Satisfactory clinical results were achieved for mean ischemic times up to 4 hours. These methods were further improved by systemic application of prostaglandins to the donor immediately before harvesting. The resulting pulmonary vasodilation caused a better distribution of the crystalloid flush with improved early postoperative graft function [19, 20].

Excellent experimental and clinical results with UWS in kidney and liver transplantation [14, 15] encouraged us to compare this solution in combination with PGI$_2$ with our current clinical standard (ECS + PGI$_2$) for pulmonary preservation in a canine transplant model after 6 hours of cold ischemia.

In our experimental setup, heterotopic heart and orthotopic single-lung transplantation was performed, as the use of extracorporeal circulation throughout the implantation can be omitted [9, 16]. Another advantage of the model is based on the separation of donor and recipient circulation, because organ deterioration will not directly lead to the recipient's death, and reperfusion can be studied more extensively.

For estimation of lung preservation quality, a 12-hour postoperative follow-up period was chosen, as shorter observation times will underestimate the damage caused by reperfusion injury. Previous studies using UWS for pulmonary preservation are therefore limited, because only single measurements after 1 hour were obtained [21, 22].

In both groups, a perfusion volume of 60 mL/kg and perfusion pressures according to the native PAP were used, because investigations by Haverich and associates [10] demonstrated advantages with regard to homogeneous fluid distribution and uniform cooling.

For quantification of lung preservation quality, left atrial pO$_2$, PAP, and PVRI were considered, whereas cardiac function was assessed using CI and LAP. Analysis of lung water content was not performed, because others have already demonstrated its lesser sensitivity when compared with functional parameters [21].

The use of UWS + PGI$_2$ for pulmonary preservation resulted in excellent postoperative oxygenation of the transplanted lung as demonstrated by improved left atrial pO$_2$ throughout the entire postoperative course compared with the ECS + PGI$_2$ group. These differences were significant after 5 hours postoperatively owing to stable pO$_2$ values in the UWS + PGI$_2$ group, whereas in the ECS + PGI$_2$ group left atrial pO$_2$ decreased significantly. This

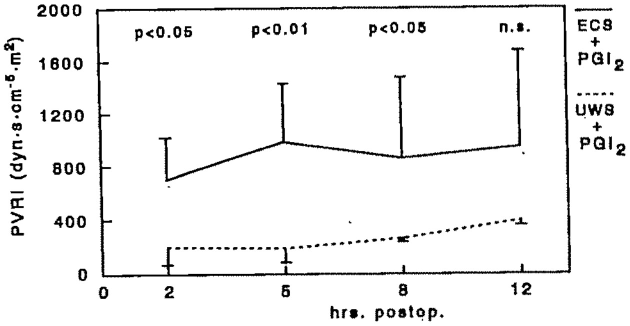

Fig 6. Postoperative donor pulmonary vascular resistance index (PVRI) values (mean ± standard deviation). (ECS = Euro-Collins solution; n.s. *= not significant;* PGI$_2$ *= prostacyclin; UWS = University of Wisconsin solution.)*

also demonstrated the necessity of an observation period of more than 6 hours for assessment of transplant lung function.

Owing to the separation of both circulations with selective drainage of the superior vena caval return in the transplanted organs, cardiac output measured postoperatively in the donor circulation represents approximately one third of the total cardiac output. For this reason CI and PVRI can be compared only within the postoperative period. Using identical myocardial protection in both groups, the initially observed higher CI in the UWS + PGI_2 group probably reflects better preservation of the pulmonary vascular bed resulting in a significantly lower PVRI during the first 8 postoperative hours, because PAP and LAP values remained low and no significant changes were observed. In the later course CI and PVRI remained stable in the ECS + PGI_2 group without significant variations, whereas a decrease in CI and increase in PVRI in the UWS + PGI_2 group might reflect some degree of impairment despite maintenance of excellent oxygenation capacity.

The basis for the improved results obtained with UWS is probably related to the structural components of the solution. In contrast to other crystalloid solutions UWS improves lung preservation in three critical aspects. Effective prevention of cell swelling and interstitial edema might be gained by the addition of three different impermeants. Especially for lactobionic acid it has been demonstrated that cell swelling is dramatically reduced during long-term perfusion with UWS [23]. Furthermore, membrane stabilization is achieved by dexamethasone in addition to the electrolyte composition [24]. Finally, antioxidants (glutathione and allopurinol) are included, which will reduce the generation of oxygen free radicals [23].

The only disadvantage to be discussed with respect to lung preservation is the high potassium concentration. This can cause vasoconstriction by smooth muscle cells in the pulmonary artery bed. Therefore, UWS was applied after administration of PGI_2. Owing to the high viscosity of this solution, a roller pump was used for application.

In conclusion, UWS in combination with PGI_2 for lung preservation provides significantly improved postoperative oxygenation and lower PVRI in lung transplantation compared with the current clinical standard as represented by ECS + PGI_2. This was demonstrated in a canine heterotopic heart and orthotopic left lung transplant model after 6 hours of cold ischemia. The superior results obtained with UWS + PGI_2 in this experimental setting suggest the introduction of UWS into clinical lung transplantation and encourage further experimental studies on prolongation of the ischemic time.

The statistical analysis was performed by R. Rohde, PhD, with the help of the Department of Biostatistics of the Hannover Medical School.

Prostacyclin was supplied by H. Loebnau, Wellcome, Großburgwedel, Germany, and the University of Wisconsin solution was kindly supplied by R. Carter, Du Pont, UK.

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DISCUSSION

DR J. KENT TRINKLE (San Antonio, TX): We have been very interested in this in the laboratory, comparing UWS with the standard "flush and slush" technique with Euro-Collins solution. Our data are quite preliminary and incomplete because the two people doing this study had to take an unexpected sabbatical to Saudi Arabia. The critical factor in the UWS, however, may be the free radical scavenger, glutathione, and we are getting good results with glutathione alone added to the flush solution. I wonder if you have looked at the individual components. This is a much easier and cheaper way to do it, to add a scavenger, rather than the whole solution.

DR JOEL D. COOPER (St. Louis, MO): Dr Trinkle, how long are you preserving lungs for with that method?

DR TRINKLE: Six hours.

DR COOPER: Okay, I am going to comment on that after you answer him. The question is, do you need the whole concoction in the UWS or are there selective components of it that might suffice?

DR HIRT: We have not evaluated special components because our endpoint is the clinical application of the solution. We therefore thought that the basic investigations had to be performed with the original fluid composition as commercially available.

DR JOSEPH LoCICERO III (Chicago, IL): Your work is extremely interesting to us because we are doing similar evaluations in an isolated, perfused, working lung model. We found that we can achieve superb protection of the parenchyma with excellent oxygenation after 17 hours of preservation with UWS. However, there is significant aerodynamic compromise, specifically, a decrease in compliance and a significant increase in resistance of the airway and work of breathing. Although this is an isolated lung preparation, we believe that there is a problem in protecting not only the large bronchus but also the small bronchus. I wonder if you have any experience in the intact animal and, if not, do you plan to evaluate the aerodynamic changes?

DR COOPER: Have you done survival models? Do you have any airway problems or signs of increased airway resistance?

DR HIRT: No, we did not observe any elevation of the inspiratory airway pressures in our experimental settings comparing UWS versus Euro-Collins solution for lung preservation.

DR COOPER: Let me abuse the prerogative of the moderator to make a couple of comments. You really were testing both cardiac and pulmonary preservation, and as you indicated, there was a difference in the cardiac index of the two groups. That has always been the problem, I believe, in looking at lung preservation by studying a model that simultaneously is dependent upon the preservation of the heart, because clearly interaction between the two is very important.

DR HIRT: Combined transplantation of heterotopic heart and adjacent left lung allows a separation of the donor and recipient pulmonary circulation. In our opinion the advantage of this model is that a deterioration in the function of the transplanted lung will not directly lead to the death of the animal, as known from single-lung transplantation with ligation of the contralateral pulmonary artery. As a consequence, the effects of reperfusion damage probably can be studied more distinctively.

DR COOPER: I think that there are a lot of very good studies, including this one, that demonstrate that one method may be better than another, but they are always limited to 6 hours. I think 6 hours is not the problem. I think there are many methods that have been clearly demonstrated to show excellent preservation of the lung in 6 hours. We too have tried UWS, and we did not find it as good as others, even the low-potassium, homemade version. It seems to me that we have reached the stage where, if you want to demonstrate that you have a method of lung preservation that is better, 12 and 24 hours is the minimum standard, because there is a whole variety of methods that give superb function after 6 hours. How long have you gone?

DR HIRT: This investigation represents our first large animal study on UWS for lung preservation with 6 hours of ischemia. For comparison with our currently used clinical standard as represented by Euro-Collins flush and ischemic times of 4 to 6 hours in the clinical situation, we did not prolong the ischemic period beyond this time in the first step. We have recently started a single-lung transplant model with UWS for extended ischemia up to 24 hours, but so far the series are too small for statements.

Normal Bronchial Healing Without Bronchial Wrapping in Canine Lung Transplantation

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Charles C. Marboe, MD, Thomas J. Kirby, MD, and Craig R. Smith, MD

Departments of Surgery and Pathology, Columbia Presbyterian Medical Center, New York, New York

The deleterious effect of steroids on bronchial healing in lung transplantation has led to the development of techniques to protect the anastomosis and to the exclusion of steroid-dependent patients from transplantation. The effect of steroids on bronchial healing was tested in a canine single-lung allotransplantation model. Twenty size-matched mongrel dogs (20 to 30 kg) underwent left lung transplantation without anastomotic wrap or direct revascularization. Postoperatively, all received daily doses of cyclosporine (15 mg/kg) and azathioprine (1 mg/kg) and were subdivided into three steroid dosage groups. Group A (n = 10) animals received 1.5 mg/kg of prednisone per day whereas groups B (n = 5) and C (n = 5) received 5.0 mg/kg of prednisone per day for 28 postoperative days. In addition, group C received prednisone (5.0 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) for 1 month preoperatively. In group A, 8 of 10 dogs survived 28 days without evidence of respiratory compromise, with anastomotic bursting pressure greater than 510 mm Hg. In group B, all 5 dogs survived to 28 days without evidence of respiratory compromise and with intact bronchial anastomoses (bursting pressures greater than 510 mm Hg). In group C, 3 of 5 animals survived to 28 days with intact anastomoses. Histological examination demonstrated normal bronchial healing in all anastomoses. These data suggest that preoperative steroid dependence should not be a contraindication to lung transplantation and that bronchial anastomotic wrapping with vascular tissue may not be essential.

(Ann Thorac Surg 1992;53:80–4)

In contrast to transplantation of other solid organs, single- and double-lung transplantation continue to be plagued with technical as well as immunologic problems. Single-lung transplantation in humans has been hampered by bronchial anastomotic complications, primarily considered a consequence of donor bronchus devascularization by the interruption of the bronchial arterial supply. Attempts at increasing bronchial blood flow by direct revascularization have met with limited success [1]. Wrapping the anastomosis with omentum has been shown to recruit arterial supply as early as the fourth postoperative day in experimental models but increases operative time and makes the procedure technically more complex [2]. The deleterious effects of steroids and other immunosuppressive agents on wound healing have been implicated as a cofactor in dehiscence. This has led to empiric exclusion of steroid-dependent patients as candidates for lung transplantation and has led to a modification in early maintenance immunosuppression, substituting antithymocyte globulins for steroids. Experimental data to support these views are scant. Therefore, in a canine single-lung allotransplant model, without bronchial wrapping, we reexamined bronchial anastomotic healing in the presence of conventional as well as suprapharmacologic doses of corticosteroids.

For editorial comment, see page 5.

Material and Methods

Under general endotracheal anesthesia, through a left thoracotomy, 20 mongrel dogs (weight, 20 to 25 kg) underwent left single-lung allotransplantation from size-matched donors. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985). All transplants were standardized to a 45-minute ischemic time in 4°C normal saline solution. Donor lungs were neither heparinized nor perfused. Lungs were preserved by submersion in normal saline solution at 4°C. The atrial anastomosis, an inverting continuous horizontal mattress suture, was performed first, followed by the pulmonary artery and bronchus anastomoses. All three anastomoses were performed using running 4-0 polypropylene suture. No attempt was made to cover, wrap, or revascularize the bronchial anastomosis. All bronchial anastomoses were immediately submerged in saline solution and tested for competence by forced ventilation through a cuffed endotracheal tube. The lung was then reexpanded, the chest incision was closed, and the dogs recovered. Postoperatively, all dogs received daily immunosuppression with cyclosporine (15 mg/kg) and azathioprine (1 mg/kg) and were subdivided into three steroid dosage groups. Group A (n = 10) received 1.5 mg/kg of prednisone daily. Groups B (n = 5) and C (n = 5) received

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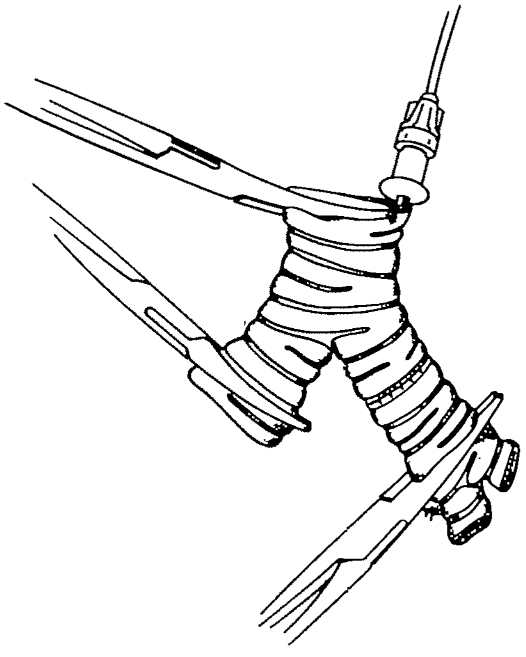

Fig 1. Preparation for measurement of bursting pressure.

5.0 mg/kg of prednisone daily. In addition, group C animals received prednisone (5.0 mg · kg^{-1} · day^{-1}) for 1 month preoperatively. All survivors were sacrificed at 28 days.

At autopsy, the bronchus was excised from 2 cm proximal to 2 cm distal to the anastomosis. The ends were cross-clamped and an 18-gauge Silastic (Dow Corning, Midland, MI) catheter was introduced into the lumen (Fig 1). Normal saline solution stained with methylene blue dye was injected into the lumen of the bronchus as intraluminal pressure was transduced to an oscilloscope. The wave form was quantitated in millimeters of mercury and calibrated before each analysis. The upper limit of measurement in this system was 510 mm Hg. The bursting pressure was the point at which methylene blue dye could be identified externally. Those that achieved the upper limit without bursting were recorded as bursting pressure greater than 510 mm Hg.

To determine the percent stenosis, the intraluminal radius was measured at the anastomosis (Anast) and at 2 cm proximal to the anastomosis (Prox). Percent stenosis was calculated according to the following formula:

$$\% \text{ Stenosis} = [1 - (\text{Anast}^2/\text{Prox}^2)] \times 100.$$

Histologic analysis of anastomoses was done after hematoxylin, phloxine, and saffron staining of paraffin section. Lung parenchyma was sectioned, and histologic characteristics were classified according to the International Society for Heart Transplantation Standardization of Nomenclature in the Diagnosis of Lung Rejection [3].

Results

Intraoperatively, all anastomoses were airtight during a sustained inflation to 40 mm Hg. Higher pressures were avoided to prevent parenchymal lung injury. In group A, 8 of 10 dogs survived 28 days without evidence of respiratory compromise. These animals had bursting pressures greater than 510 mm Hg. Two dogs died 6 and 9 days postoperatively as a result of left atrial thrombosis. These animals demonstrated intact bronchial anastomoses at autopsy (bursting pressures of 303 and 475 mm Hg, respectively). In group B, all 5 dogs survived to 28 days without evidence of respiratory compromise and with intact bronchial anastomoses (bursting pressures greater than 510 mm Hg). In group C, 3 of five animals survived 28 days. The 3 survivors had intact anastomoses at autopsy (bursting pressures greater than 510 mm Hg). One dog exsanguinated from a gastroduodenal ulcer on the first postoperative day and bursting pressure was not obtained. The other died on the thirteenth postoperative day of congestive heart failure resulting from an intraoperative myocardial infarction sustained during pulmonary artery injury. This animal had a bronchial anastomotic bursting pressure of 185 mm Hg.

Anastomotic histology was considered normal if regenerated epithelium was observed lining the lumen with normal scar formation and healing fibrosis deep to the anastomotic site. This was seen in all anastomoses, including all three with bursting pressures less than 510 mm Hg, and in 3 animals with mild, moderate, and severe rejection as graded by the International Society for Heart Transplantation Standard of Nomenclature [3]. The animal with severe (A4a) rejection, despite extensive bronchiolitis obliterans, had a bursting pressure greater than 510 mm Hg with no evidence of bronchial dehiscence. No manifestations of clinically significant stenosis, such as stridor, respiratory distress, or atelectasis, were detected in any animal. In groups B and C the average stenosis, as calculated by the formula in the Material and Methods section, was 19.1% (range, 14.3% to 20.3%).

Comment

Concern over the fate of the healing bronchial anastomosis in lung transplantation has existed since investigation in this arena began [4, 5]. Of the first 38 clinical lung transplantations done in the world, only 16 patients were alive beyond 10 days. Of these 16 patients, 10 died of bronchial complications within 7 months [5]. This experience prompted extensive research into the etiologic factors associated with bronchial dehiscence in lung transplantation. Early contributions to improve bronchial healing included wrapping the anastomosis with perihilar connective tissue [6], telescoping the bronchial ends [7], shortening the length of the donor bronchus [8], and bronchial artery reanastomosis [1, 9]. Particularly for the latter, which remains a difficult technical problem, application of these advances produced marginal improvement in results.

This led to the landmark work of Cooper and his colleagues in Toronto, who demonstrated in a canine autotransplant model that omentum can bring saturated blood to the anastomosis in the early postoperative period [2, 10]. Related studies suggested a deleterious effect of methylprednisolone on bronchial healing when compared with a cyclosporine group or with nonimmunosuppressed controls [11, 12]. This experimental work led directly to the first successful series of single-lung transplants [13] and established three principles of clinical practice: (1) to wrap all bronchial anastomoses with omentum, (2) to avoid postoperative steroids, and (3) to deny transplantation to patients dependent on steroids for treatment of their underlying lung disease.

There are serious disadvantages to these principles. Mobilizing omentum requires a laparotomy, which adds the risk of pulmonary and other complications in an immunocompromised host. Omentum must be passed through a diaphragmatic defect, which can become a clinically significant hernia [2]. When maintenance immunosuppression is modified by substitution of antithymocyte globulins for steroids, the risk of viral and fungal infection is increased. Finally, many patients who might otherwise be good candidates for lung transplantation are steroid dependent and are denied lung transplantation until withdrawn from steroid treatment.

For these reasons, this study was undertaken to reexamine these concepts. This study differs in several respects from the important work by Cooper and his colleagues in Toronto. In one series of experiments they compared anastomoses with omental wrapping to those without and reported that wrapped anastomoses had improved gross and histologic appearance, reduced bronchial stenosis, and neovascularity arising from the omentum demonstrated on celiac arteriography [2]. However, because arteriography was not performed in the unwrapped animals, the amount of neovascularity achieved without omental wrap cannot be determined. The present study was not designed to compare wrapped with unwrapped animals, but the histologic appearance and percent stenosis of the unwrapped anastomoses in all three steroid dosage groups was consistent with normal healing.

In the present study, bursting pressure was measured to quantitate the strength of the anastomosis, whereas tensile strength was measured in the Cooper studies. Tensile strength reflects resistance to disruption by linear forces, as if the lung were simply a weight hanging from the anastomosis, and was found to be decreased by steroids [11]. Linear forces are probably minimal in a lung that fills the hemithorax. Our use of bursting pressure for measurement of the integrity of the anastomosis reflects our dissatisfaction with the tensile strength method, which measures only linear forces. Bursting pressure reflects resistance to disruption by radial forces generated within the lumen and is analogous to the airway pressure generated during cough or positive pressure ventilation, perhaps a more clinically relevant measurement. Data to support this contention are not currently available. In the present study the maximum intraluminal pressure applied (>510 mm Hg) is far in excess of the maximum physiologic pressure of 100 to 120 mm Hg [14] and was accepted as evidence of excellent anastomotic strength. The 3 animals with bursting pressures less than 510 mm Hg still had bursting pressures well above the usual physiologic range (185, 303, and 475 mm Hg). The animal with the lowest bursting pressure measured (185 mm Hg) was sacrificed after 13 days of low cardiac output following intraoperative myocardial infarction.

In a limited cross-comparison between bursting pressure and tensometry, 3 animals with bursting pressures greater than 510 mm Hg were found to have a bronchial tensile strength (1,064 ± 282 g) that correlated with those considered to be in the satisfactory range in the Cooper study (1,232 ± 101 g) [12].

Finally, it is particularly noteworthy that bronchial dehiscence was not seen in any animal in this allograft study or in the Cooper autograft studies, and all animals in the latter survived without incident to sacrifice at 23 days, regardless of histologic or arteriographic findings [2]. None of the three deaths in this study was related to bronchial healing. Satisfactory healing was seen even in the presence of severe pulmonary rejection and bronchiolitis obliterans.

In summary, the data in this canine allograft model suggest that steroid immunosuppression is compatible with excellent bronchial healing, even at higher than conventional dosage. Preoperative steroid administration, at sufficiently high dosage levels to produce gastrointestinal ulceration and bleeding in more than 1 experimental animal, did not have deleterious effects on bronchial healing. Finally, excellent healing was obtained without wrapping the anastomoses with omentum or with any other material.

It would be hazardous to conclude that bronchial healing is no longer a problem in lung transplantation, as recent experience has demonstrated [15]. Although previous studies may have overemphasized the detrimental effects of steroid, or the importance of omental wrapping, the bronchial anastomosis is undeniably hypovascular unless bronchial arteries are rejoined [16]. In a clinical allograft, lung preservation, ischemic time, rejection, infection, and the hemodynamic stability of the recipient undoubtedly play a role in bronchial healing, and it will always be difficult to isolate the contribution of each variable. Vascular wraps are still receiving appropriate experimental attention [17], and attempts are being made to simplify bronchial artery anastomosis [18]. In addition, the advantages of a telescoping anastomosis have been reported especially in patients receiving steroids [19]. Continued evolution of the basic principles of bronchial healing can be expected.

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DISCUSSION

DR HANI SHENNIB (Montreal, Que, Canada): I enjoyed your paper very much. This is an elegant experimental model to show that steroids are not necessarily detrimental to the healing of the airway. However, we have looked at our own patients in 20 lung transplantations that were done in the last year and a few months, and the average steroid dose that we have given was about 6.8 mg/kg body weight every day over the first 2 weeks. So even clinically, and at least from the data from Trinkle in San Antonio, the effect of steroids does not seem to be that bad.

I, however, have a question in regard to the bursting pressure. I noticed that in your animal model you used Prolene. We do not use Prolene, we use Maxon and Vicryl, and I am just wondering whether the bursting pressure actually tests the actual healing of tissue or tests the actual strength of the suture material?

DR AUTERI: We did not take out the suture material. In those animals where it did burst at lower than 510 mm Hg—303, 475, and 185 mm Hg—it burst between sutures, and we think, given this model, we can see a small pinhole burst that could occur between sutures. I should also note that we listed some anastomoses as "greater than 510 mm Hg" because that was the limit of our apparatus. However, in some of those the burst occurred at sites other than the anastomosis, indicating a very strong anastomosis.

DR STEPHAN W. HIRT (Hannover, Germany): I would like to congratulate Dr Auteri and his associates for their study and would like to comment on our clinical lung transplant experience. In the last 2 years we have accepted recipients with a regular daily dose of prednisone up to 20 mg, and recently we use no bronchial wrapping. Reviewing the last 27 single-lung and 6 double-lung transplants, we have observed only one limited dehiscence of a bronchial anastomosis in a patient with a double-lung transplant who was not receiving corticosteroids before transplantation and did not receive postoperative steroids for 6 weeks.

DR J KENT TRINKLE (San Antonio, TX): I enjoyed your paper because it parallels our clinical experience. When I first started doing transplantation in patients who were receiving prednisone and giving them large doses of methylprednisolone postoperatively, everybody thought I was crazy.

We have done 37 single-lung transplantations with no bronchial complications, neither stenosis nor dehiscence. I think it is a multifactorial thing. About two thirds of our patients are receiving preoperative prednisone and many of them would have died if we had weaned them off of prednisone. So I think that is an important point. We have also kept all of our patients on large-dose methylprednisolone regimens for the first 3 days, and then they receive 1 mg/kg of prednisone for a week, which is tapered to 0.75, 0.5 $\mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$, and so forth at weekly intervals.

I think the telescoping technique is important, as is keeping the bronchial stump short. Prolene sutures are also important, and I think steroids may improve bronchial healing. Now, in the patients in whom we perform bronchoscopy we see an unusual phenomena: the donor bronchial mucosa is not pale like you sometimes see in trauma cases or in sleeve resections for carcinoma. Instead, the distal bronchus tends to be a little pinker or more hyperemic. And I think—the key word there is think—that the steroids preventing rejection may maintain that vascularity.

DR JOHN W. FEHRENBACHER (Indianapolis, IN): Just a concern. I may be personally brainwashed by Dr Cooper teaching us. I am still concerned that the dogs were receiving steroids for only a month preoperatively. It has been my clinical impression with some of these patients who receive steroids for a year or 2 years that you can just tell by looking at their skin changes and such, and you really worry about healing. Do you have any comments on that?

DR AUTERI: I am unable to quantitate exactly how much steroid was on board. We did not have steroid dosage levels. And a fault of this study compared with Dr Cooper's study was that skin incisions were made in the latter to test if steroid levels were in fact adequate. I can say that, at least subjectively looking at the tissues, the tissues were what I would call steroid tissues, very friable, very much unable to hold a stitch, clearly steroid tissues.

In addition, I should note that in group C, the group that received preoperative 1-month steroid treatment, all 5 of the animals, 1 of which died of a gastrointestinal bleed, had some evidence of hemorrhage from the gastrointestinal tract and needed H_2 blockers and antacids.

DR JOEL D. COOPER (St. Louis, MO): But in fairness, you were using a much greater than clinical dose.

DR AUTERI: Yes.

DR COOPER: So you were really stressing your model, because the studies we did used a dose of 2 mg/kg, and nobody uses that much anymore; it is usually 0.5 mg/kg. So in fairness to your model, you were really using a very high-dose steroid.

DR PAUL F. WATERS (Los Angeles, CA): Did I hear you say that the ischemic time on your transplants was 45 minutes?

DR AUTERI: That is correct.

DR WATERS: I wonder if that is not a little short considering that I do not think many of us can do a lung transplantation in 45 minutes. I wonder if it might have been more clinically relevant to employ a longer ischemic time.

DR AUTERI: I can say these were done side by side in the same room, and the recipient hilum was dissected—most of the work was done on the recipient hilum—and so it was a matter of sewing it in in 45 minutes. It was out and back in again in 45 minutes. We chose 45 minutes to eliminate any effect preservation would have on bronchial healing. We wished only to test the effect of steroids on bronchial healing.

DR COOPER: Let met ask you. When you just eyeballed your anastomoses—forgetting about the strength, et cetera—did they look normal and healed?

DR AUTERI: I think the strongest point here is that yes, in fact they looked very strong, and I was on the other end of that catheter and pushing quite hard in that study.

DR COOPER: But when you opened up the bronchus and looked at the anastomosis, you were satisfied?

DR AUTERI: Yes.

DR COOPER: I think, frankly, that is probably more important than anything else.

My general feeling is that in the early days of transplantation, as you have pointed out, things were multifactorial—preservation was not the best, patients were on ventilators for long periods of time, infection was more common—and I think that in the early days, to get things going, there were a lot of extra security measures that maybe we and others took. I think what your work points out, and what the work that Dr Trinkle and the Hannover group and Toronto and others have done has pointed out, is that probably these days the need for the omentum and the avoidance of early steroid treatment are no longer as important as perhaps they were to get things going. We still use the omentum, but certainly we do cases without it if it is not available, and we will take people receiving low-dose steroids. We have not started as early as other people have suggested. But I think the scene has changed.

We have an international registry of about 510 cases in it that we follow up. I just looked the other day, and the death rate from airway complications is less than 5% in that group. And so I think that the situation has changed considerably, and I think your paper is a very important contribution. Thank you for it.

Pleuroperitoneal Shunts for Refractory Chylothorax After Operation for Congenital Heart Disease

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Between 1980 and 1990, 10 of 12 children with a symptomatic chylothorax after operation for congenital heart disease failed to respond to traditional medical therapy (thoracentesis, tube thoracostomy, low-fat diet). All 10 patients underwent placement of a pleuroperitoneal shunt, with complete resolution of the chylothorax in 9 patients (90%). Cardiac catheterization, performed before placement of the pleuroperitoneal shunt in 5 patients, demonstrated elevated right atrial pressure in all patients (range, 10 to 25 mm Hg). The pleuroperitoneal shunt functioned effectively in 4 patients with moderately elevated right atrial pressures (range, 10 to 16 mm Hg; median, 13.5 mm Hg) but not in 1 patient with a right atrial pressure of 25 mm Hg. Pleuroperitoneal shunting as treatment for chylothorax after operation for congenital heart disease is safe and effective, even in the face of moderate elevations in right atrial pressure.

(Ann Thorac Surg 1992;53:85–7)

Persistent chylothorax is a recognized complication of operation for congenital heart disease and may occur secondary to trauma to the thoracic duct, caval obstruction, or elevated central venous pressures. Medical therapy (low-fat diet, supplementation with medium-chain triglycerides, intravenous alimentation, tube thoracostomy) has a high failure rate (>75%) and may be accompanied by respiratory compromise, lymphopenia, and protein deficiency [1, 2]. Reexpansion of the lung on the affected side serves both to relieve symptoms of respiratory distress and to tamponade the thoracic duct [1]. Late reaccumulation of chylous effusions may occur, and prolonged hospitalization (often exceeding 6 weeks) may be necessary before successful resolution of the chylothorax.

Traditional therapy for chylothorax that is refractory to tube drainage has included pleurodesis and thoracotomy with ligation of the thoracic duct. Anatomic variants limit the success of thoracic duct ligation in many cases, and reaccumulation of chylous effusions may occur after apparently successful thoracic duct ligation [3]. In 1982, Weese and Schouten [4] introduced the use of the pleuroperitoneal shunt as treatment for malignant pleural effusions in adults.

Since 1983, we have used pleuroperitoneal shunts as surgical treatment for refractory chylothorax in children, and have previously reported our preliminary experience with this technique, including 6 children with chylothorax after operation for congenital heart disease [5–7]. Other investigators have questioned the effectiveness of pleuroperitoneal shunting in this subset of patients, who may have elevated right atrial pressures during the postoperative period [8]. Concern has been raised that elevated right atrial pressures transmitted to the peritoneal venous and lymphatic bed may impair absorption of shunted chyle. We report the successful use of the pleuroperitoneal shunt in patients after operation for congenital heart disease, even in the face of moderate elevations in right atrial pressure.

Material and Methods

We reviewed the records of 879 patients with congenital heart disease who underwent cardiac operation at the University of Virginia between June 1980 and June 1990. During this period of time, a symptomatic chylothorax developed in 12 patients (1.3%) after operation for congenital heart disease. The diagnosis of chylothorax was made when a pleural effusion developed that was milky in appearance with an elevated triglyceride level or a lymphocyte count greater than 90%, or if a serous pleural effusion with the same chemical and cellular characteristics developed in a nonfed patient. Age; diagnosis; operative procedure; volume, onset, and duration of pleural drainage; and right atrial pressure at cardiac catheterization before pleuroperitoneal shunting are indicated in Table 1. In all patients, respiratory compromise was initially treated with tube thoracostomy. Nutritional support was maintained by intravenous alimentation or a low fat diet. When pleural drainage failed to diminish after a period of at least 10 days, patients underwent placement of a pleuroperitoneal shunt.

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Table 1. Characteristics of Patients Requiring Pleuroperitoneal Shunts

Patient No.	Diagnosis	Operation	Age (mo)	Onset of Effusion (days postop)	Daily Volume (mL/kg)	RA Pressure (mm Hg)	Days to Shunt	Days to Discharge	Months to Removal
1	d-TGA	Senning	8	9	29	. . .	11	11	5
2	Pulmonary atresia	Central shunt	0.25	4	10	. . .	11	41	Died
3	AV canal	Repair	9	2	22	. . .	15	20	8
4	Single ventricle	Fontan	42	1	23	15	13	14	7
5	Pulmonary atresia	Fontan	17	43	27	. . .	21	6	4
6	d-TGA	Senning	12	3	17	16	18	49	9
7	Tetralogy, residual VSD	Repair	19	2	90	25	57	Died	. . .
8	d-TGA	Senning	8	3	6	. . .	28	15	3
9	d-TGA	Senning	18	6	16	10	31	15	10
10	d-TGA	Revision of Mustard	5	1	13	12	27	10	4
Median			10.5	3.5	19.5	15	19.5	15	7

AV = atrioventricular; d-TGA = dextrotransposition of the great arteries; RA = right atrial; VSD = ventricular septal defect.

Results

A symptomatic chylothorax developed in 12 patients 1 to 43 days (median, 3.5 days) postoperatively. A chylous pleural and pericardial effusion did not develop in 1 patient (patient 5) until 6 weeks after an uncomplicated Fontan operation. Medical therapy was successful in 2 patients (17%) within 2 weeks of the onset of the effusion. Chylous effusions necessitating surgical therapy persisted in 10 children (83%), who subsequently underwent placement of a pleuroperitoneal shunt 11 to 57 days (median, 19.5 days) after the onset of the effusion and 14 to 64 days (median, 30.5 days) after the initial operation. The procedure was successful in draining the pleural effusion in 9 of 10 patients (90%) but failed to relieve the effusion in 1 patient who had undergone repair of tetralogy of Fallot 57 days before shunt placement. This patient's right atrial pressure was 25 mm Hg at postoperative cardiac catheterization. He had a large residual ventricular septal defect and ultimately died of sepsis and low cardiac output after reclosure of his ventricular septal defect.

Of the 9 surviving patients, right atrial pressure measurements were documented at postoperative cardiac catheterization in 4 patients and ranged from 10 to 16 mm Hg (median, 13.5 mm Hg). Of the 5 patients with transposition of the great arteries, cardiac catheterization was performed in 3 and showed mild baffle obstruction (mean gradient from superior vena cava to right atrium was 4 mm Hg). Discharge from the hospital occurred 6 to 49 days (median, 15 days) after placement of the pleuroperitoneal shunt. The frequency of manual pumping was gradually decreased over a period of months, and in 8 of the 9 successful cases, the shunt was removed electively 2.5 to 10 months (median, 7 months) after placement without reaccumulation of effusion. The 1 patient whose shunt was not removed died of extreme hypoxemia secondary to pulmonary artery hypoplasia 4 months after the central shunt and 1 month after placement of a modified Blalock-Taussig shunt. She had no pleural effusion before her death, and the shunt had not been pumped in weeks.

Comment

Pleuroperitoneal shunting offers an effective means of reducing respiratory symptoms in patients with chylothorax after operation for congenital heart disease while preventing the extreme protein, lipid, and lymphocyte depletion that accompanies tube thoracostomy. The only hemodynamic contraindication is a markedly elevated right atrial pressure. Pleuroperitoneal shunting was effective in 4 patients with a moderately elevated right atrial pressure but not in 1 patient with a right atrial pressure of 25 mm Hg. We postulate, as have others, that markedly elevated right atrial pressures transmitted to the venous and lymphatic bed of the peritoneal space may impair absorption of shunted pleural fluid [8].

Pleuroperitoneal shunting is not a substitute for postoperative hemodynamic investigation or, if necessary, reoperation. However, if there are no simple medical or surgical options, placement of a pleuroperitoneal shunt is preferable to thoracic duct ligation, pleurodesis, or prolonged chest tube drainage. We now recommend early intervention (after 7 to 10 days) in patients with serious chylous effusions that fail to regress with medical therapy.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Bronchial Revascularization in Double-Lung Transplantation: A Series of 8 Patients

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Donor airway ischemia is the main cause for defective tracheal or bronchial healing after double-lung transplantation. Anatomical studies and bronchial arteriograms have shown that the right intercostal bronchial artery is constant (95% of instances) and provides an important blood supply to the distal trachea, the carina, and the right bronchial tree as well as to the left side through a subcarinal and periadventitial anastomostic network. To maintain this important bilateral bronchial circulation, it is of capital importance not to mobilize the arteries individually and to avoid large dissections around the carina. Both bronchi can thus be revascularized by indirect aortic reimplantation using a bypass graft to a single aortic patch that includes the origin of the right intercostal bronchial artery. Furthermore, the origin of other vessels (a common trunk and left arteries) can be found within a short distance of the right intercostal bronchial artery and possibly be contained within the same aortic patch. From a series of 56 lung transplantations, 8 patients underwent restoration of the bronchial vascularization using a recipient saphenous vein graft between the donor bronchial arteries and the anterior aspect of the recipient's ascending aorta. A lower tracheal anastomosis was performed. Bronchial arterial blood supply was evaluated both by endoscopy and by arteriography at about the 15th postoperative day. The bronchial circulation was visualized at this time in five of seven arteriographies, and this was associated with excellent tracheal healing in all 8 patients.

(Ann Thorac Surg 1992;53:88–94)

Tracheal or bronchial healing represents one of the most critical problems in human lung transplantation, and impaired healing may be seen after any form of transplantation. Ischemic airway complications have been reported after about 10% of heart-lung transplantations [1]; the incidence may reach 20% after single-lung transplantation [2], and may be as high as 40% after en-bloc double-lung transplantation with tracheal anastomosis [2]. In double-lung transplantation, clinical experience with bilateral bronchial rather than single tracheal anastomosis has been more satisfactory in this regard, reducing but not suppressing the occurrence of ischemic complications [3, 4]. The incidence of these complications remains high enough for some groups to prefer heart-lung over double-lung transplantation [5–7] and then use the recipient's heart as a donor heart for another recipient (domino procedure).

Recent bronchoscopic evaluation of tracheobronchial healing in 40 patients who underwent transplantation has shown us that among all factors affecting healing at the anastomotic site, insufficient blood supply (that is, donor tracheobronchial ischemia) was the most important [8]. These observations led us to consider that, as outlined by Robicsek, it makes as little sense to transplant lungs without reconstituting the bronchial arterial supply as to transplant a heart without its coronary arteries. Feasibility of such revascularization was demonstrated as early as in 1950 by Metras [9] and was confirmed in animal experiments in 1970 by Mills and associates [10], who showed that after bronchial circulation was restored, bronchial healing was much improved.

From these considerations, it became obvious that revascularization of bronchial arteries was mandatory in double-lung transplantation, either with bilateral bronchial or single tracheal anastomosis.

Material and Methods

Our surgical protocol for revascularization of bronchial arteries was preceded by an anatomical study of the tracheobronchial arterial blood supply in humans from 20 anatomical dissections and from 50 angiographic studies in thoracic surgical patients. From these studies it appeared that: (1) The right intercostobronchial artery (RICBA) is the most constant (95% of cases) arterial supply as well as the most important as it directly feeds the right main bronchus, the distal rings of the trachea, and the carina. It also supplies the left main bronchus through subcarinal collaterals and a network of small vessels coursing in periaortic adventitial and peritracheobronchial tissues. Assuming that this anastomotic net-

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work is not disrupted during extensive dissection or isolation of the arterial pedicle, revascularization with the RICBA should be sufficient to supply the whole proximal tracheobronchial tree. (2) A common bronchial arterial trunk to the right and left sides was found in about half of the cases. (3) One or two other smaller bronchial arteries supply the left main bronchus but do not appear to be essential. (4) In 50% of cases, orifices of many bronchial arteries originating from the anterolateral wall of the thoracic descending aorta are located within 0.5 to 1.5 cm of the RICBA ostium, thus possibly allowing simultaneous direct revascularization of two to three bronchial arteries with a single aortic graft during implantation.

As a result of this study, we have defined the following goals for the operative procedure: (1) revascularization of the RICBA or of a common arterial trunk of the same or larger size and revascularization of an additional artery if its orifice is in proximity of the main vessel; (2) airway anastomosis at the tracheal supracarinal level, as this area appears to have the most constant blood supply and as preservation of the carina maintains the subcarinal and pericarinal arterial anastomotic network between the right and the left main bronchi; and (3) preservation of all peritracheobronchial arterial anastomoses by avoiding inappropriate mobilization and dissection of the arterial trunks. To meet these requirements, in situ revascularization of the left posterolateral aspect of the double-lung block is provided by indirect aortic reimplantation using an autologous saphenous vein graft. The fish-mouthed distal implantation of the graft is made ex vivo on the dorsal part of the transplant. The proximal anastomosis on the aorta is performed at the end of the procedure after all the steps of implantation have been completed.

The sequence of procedures to be performed in this surgical technique is as follows: In the recipient, a saphenous vein graft 15 cm in length is harvested from the thigh before the thoracic operative field is prepared, and the graft is maintained in cold saline solution. In the donor, harvesting of the heart-lung block includes the thoracic aorta, the esophagus, and all fatty and mediastinal vascular tissues overlying the vertebral column, according to the technique described by Schreinemakers and associates [11]. The donor heart is then removed ex vivo in order not to weaken the block before it is extracted from the mediastinum. After transportation, the graft is prepared in an operating room adjoining the recipient operating room. This entails stripping of the esophagus with meticulous hemostasis; longitudinal opening of the aortic segment and identification of the bronchial arterial orifices; preparation of an aortic patch around the origin of the RICBA, possibly including one or more additional bronchial arteries that originate in the vicinity; ex vivo distal anastomosis of the saphenous graft on the aortic patch using a running 6-0 Prolene suture (Ethicon, Somerville, NJ); meticulous hemostasis of the mediastinum verified by serum infusion through the saphenous graft and complementary use of fibrin sealant on dissected areas; and implantation of the double-lung block. A low supracarinal tracheal anastomosis is made and then wrapped in the recipient's surrounding mediastinal tissues. Aortic cross-clamping and infusion of cardioplegic solution (Brechtneider's) are performed to allow left atrial and main pulmonary artery anastomosis, and finally, proximal anastomosis of the saphenous vein graft on the left anterolateral aspect of the ascending aorta is performed. Depending on the duration of donor lung ischemia, this may be performed either while the heart is still arrested or after it has been resuscitated. Hemostasis and immediate patency of the saphenous vein graft can easily be verified in the posterosuperior mediastinal area as well as in the left suprahilar and infrahilar areas. We have never had problems with hemostasis at any level on the graft.

Bronchial healing was assessed through endoscopic and angiographic controls. At endoscopic examination on days 15 and 30, and at 6 months if possible, healing was qualified as grade I to IV according to criteria defined in a previous staging study [8]:

Grade I: healthy mucomucosal healing similar to that seen after autologous tracheobronchial anastomosis. After lung transplantation this type is uncommon (6 of 34 cases)

Grade II: delayed mucomucosal healing without necrosis. A mucosal healing without sequelae occurs after 4 to 6 weeks and follows tracheal wall and peritracheobronchial healing. Grade II is the most common type of uncomplicated healing (15 of 34 cases)

Grade III: defined by the occurrence of necrosis affecting the mucosa and the tracheal wall at various depths in a complicated cicatrization. These lesions are associated with serious ischemia (13 of 34 cases), mainly after single-lung and double-lung transplantation. Airway survival thus depends strictly on healing through the peritracheobronchial wrap. Anastomotic leaks, fistulas, stenoses, and malacia are the consequences of these ischemic lesions

Grade IV: characterized by ulcerations and necrosis in areas distant from the anastomosis and occurring mainly on the carina and bronchial spurs. These eventually heal without sequelae.

Angiographic studies included selective opacification of the venous graft and the revascularized bronchial arteries, and were performed between the 15th and the 30th postoperative day. Laser Doppler velocimetry evaluation of the mucosal blood flow in the transplanted bronchial tree was performed on the 8th postoperative day in the most recent patient.

Case Reports

From May 1990 to February 1991, 8 patients have undergone double-lung transplantation with revascularization of bronchial arteries according to this technique. Follow-up of these patients ranges from 2 to 11 months postoperatively. Revascularization was also achieved successfully using a slightly different technique in a single right lung transplant, which is not included in this report.

All patients but 1 have received our current immunosuppressive protocol, which consists of rabbit antithymocyte globulin, 3 mg · kg^{-1} · day^{-1} during the first 7 days; cyclosporine A, 3 mg · kg^{-1} · day^{-1} intravenously from the first to the fifth postoperative day, then 8 to 10 mg · kg^{-1} · day^{-1} by mouth; azathioprine, 1 to 2 mg · kg^{-1} · day^{-1} from day 1 to day 10, after which administration is stopped until day 60, when it is reinstituted; and prednisone, 0.5 to 1 mg · kg^{-1} · day^{-1} from the 7th postoperative day on. Acute rejection episodes were treated with intravenous bolus of methylprednisolone (3 g over 3 days). Low-level anticoagulation using subcutaneous calcium heparin or enoxaparine (Lovenox) was started as soon as the recipient coagulation controls had returned to normal.

Patient 1

A 48-year-old man with panlobular emphysema underwent double-lung transplantation with tracheal anastomosis and RICBA revascularization on May 19, 1990. Overall ischemic time was 285 minutes. The immediate postoperative course was uneventful, and the patient was extubated on the 24th postoperative hour. In addition to the usual immunosuppressive protocol, intravenous methylprednisolone (3 g) was given with success from the 9th to the 11th postoperative day for an episode of acute rejection. Initial bronchoscopic survey of the airway showed excellent vascularization and good trophicity. On the 15th day, there was perfect grade I healing of the posterior tracheal membrane and good grade II healing on the cartilaginous ring (Fig 1). Anticoagulation was discontinued on the 16th day, and control angiography showed proximal thrombotic aortobronchial graft occlusion. However, the patient did well and was discharged from the hospital on the 30th postoperative day with excellent functional progression and general status. Bronchoscopic controls at 1, 3, and 6 months showed a healthy nonstenotic, well-epithelialized anastomosis.

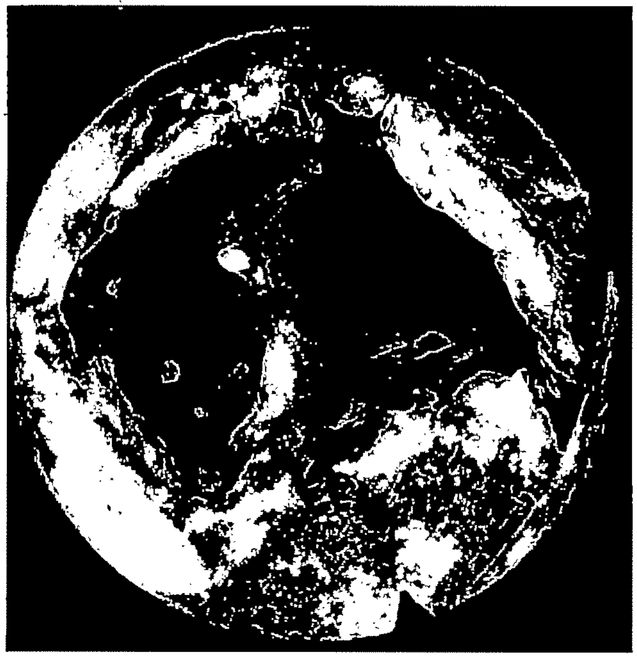

Fig 1. (Patient 1.) Endoscopic view showing good tracheal healing (15th postoperative day) despite a secondary thrombosis of the graft.

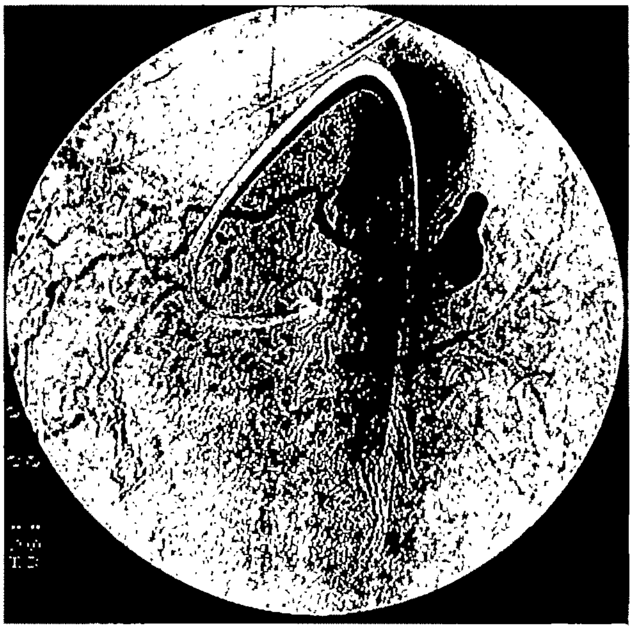

Fig 2. (Patient 2.) Arteriogram at 16 days showing the patency of the saphenous graft and good revascularization of the right intercostobronchial artery and of two other bronchial arteries.

Patient 2

A 36-year-old man who sustained acute paraquat poisoning on June 6, 1990, underwent on June 13 double-lung transplantation with simultaneous revascularization of the RICBA, of a left bronchial artery, and of a small intermediate artery. Ischemic time was 210 minutes. Postoperatively the patient received OKT3 and steroids for immunosuppression because of paraquat-related kidney and marrow intoxication justifying the avoidance of cyclosporine A and azathioprine and their potential side effects. The usual immunosuppressive therapy was initiated during the second week. Postoperatively lung function was immediately satisfactory but, because of residual intoxication, the patient was extubated only on the 4th postoperative day when biological analysis had progressively returned to normal. Bronchoscopic survey on the first day showed a well-colored and vascularized tracheobronchial tree, and on the 14th day perfect grade I healing of the whole anastomotic circumference was seen. Control saphenous vein graft angiography showed excellent opacification of the three revascularized bronchial arteries (Fig 2). On the 30th day total healing was achieved without any degree of stenosis. Unfortunately, the patient died soon after of the consequences of his poisoning.

Patient 3

On July 7, 1990, a 55-year-old woman underwent double-lung transplantation and revascularization of the RICBA for pulmonary fibrosis. Ischemic time was 240 minutes.

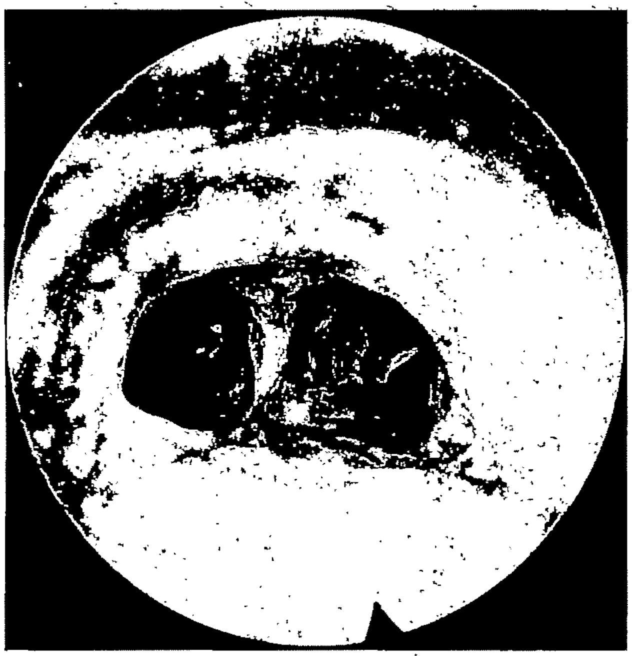

Fig 3. (Patient 3.) Endoscopic view at 6 months showing adequate epithelialization and size of the tracheal anastomosis.

The patient received standard immunosuppression. Pulmonary function was immediately satisfactory but, owing to a clotted hemothorax needing right thoracotomy in the 24th hour, extubation was delayed until the 48th hour. This bleeding from a dense posterior pleural symphysis of the right pleural cavity was unrelated to the site and the technique of revascularization. An acute rejection episode was treated between the 10th and the 12th postoperative days. Endoscopic survey showed good trophicity of the donor tracheobronchial tree and, on the 15th day, good grade II healing of the tracheal anastomosis. Nevertheless, control angiography demonstrated distal thrombosis of the vein graft after discontinuation of the anticoagulant therapy. The postoperative course was, however, quite satisfactory. At control examinations in the 1st, 3rd, and 8th postoperative months, the anastomosis appeared very healthy with good epithelialization and without any stenosis (Fig 3).

Patient 4

A 55-year-old man with pulmonary fibrosis associated with scleroderma underwent double-lung transplantation on Dec 2, 1990, with concomitant revascularization of a right and left common bronchial arterial trunk. Ischemic time was 280 minutes. The postoperative course was uneventful, and the patient was extubated in the 24th postoperative hour. Tracheal endoscopic examination showed good trophicity of the donor bronchi and, on the 15th day, excellent tracheal healing (grade I on the posterior membrane and grade II on the cartilaginous ring). Control angiography on the 17th day showed patency of the graft revascularizing the bronchial arterial trunk (Fig 4). The patient was discharged on the 35th day with a well-epithelialized and normal-sized tracheal anastomosis.

Patient 5

A 53-year-old woman with end-stage lung disease due to bilateral emphysema underwent double-lung transplantation with revascularization of the RICBA on Jan 4, 1991. Ischemic time was 225 minutes. The patient received standard immunosuppression with additional prednisone (20 mg/day) because she had been steroid dependent for the last 2 years. She was extubated in the 24th hour, and endoscopic survey showed good evolution of the tracheal healing (grade II), as confirmed on the tomographic film (Fig 5). Control angiography on the 27th postoperative day showed a patent graft with opacification of the bronchial arteries.

Patient 6

A 41-year-old man with bilateral bronchiectasis underwent double lung-transplantation with tracheal anastomosis and RICBA revascularization on Jan 31, 1991. Ischemic time was 235 minutes. Despite the necessity of a left thoracotomy 6 hours postoperatively for posterior pleural bleeding, he was extubated on the 24th hour. The postoperative course was uneventful, and trophicity of the donor bronchial tree was excellent. Tracheal healing was grade I on the 15th postoperative day, and the angiographic study on the 20th day confirmed good perfusion of the graft and of the bronchial arteries (Fig 6).

Patient 7

A 19-year-old man with cystic fibrosis underwent double-lung transplantation with revascularization of the RICBA on Feb 16, 1991. Ischemic time was 240 minutes. His

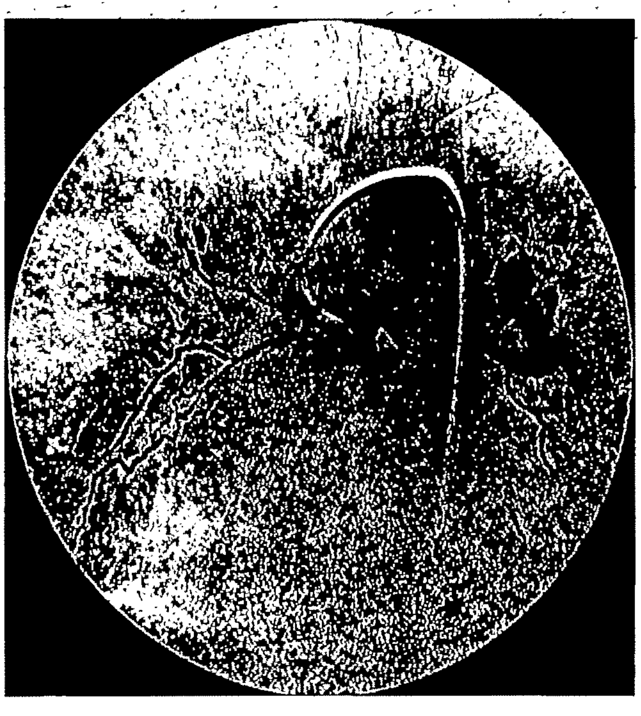

Fig 4. (Patient 4.) Bronchial arteriogram at day 17 showing good patency of the graft feeding the bronchial tree through a common arterial trunk (atrophic right intercostobronchial artery).

respiratory function was immediately adequate, and he was extubated in the 20th postoperative hour. Tracheal healing was excellent (grade I on the 15th postoperative day), and control angiography on the 24th day showed patency of the graft and of the bronchial arteries.

Patient 8

A 63-year-old woman with emphysema and bronchiectasis underwent double-lung transplantation and bronchial artery revascularization on Feb 22, 1991. Ischemic time was 230 minutes. Her postoperative course was uneventful, and she was extubated in the 36th hour. The peri-anastomotic mucosal blood flow was assessed by laser Doppler velocimetry [12] on the 8th postoperative day and was found to be adequate (Fig 7). Control endoscopy of tracheal healing on the 15th day showed grade I despite a very stormy evolution: she experienced an episode of acute rejection on day 10; after successful control with an intravenous bolus of steroids, rejection rapidly recurred at day 17 and necessitated treatment with OKT3 from day 18 to day 28 and permanent ventilatory support. Bilateral pneumonia with recurrence of resistant *Pseudomonas aeruginosa* impeded the weaning of the patient from support, and she died of septicemia on day 35.

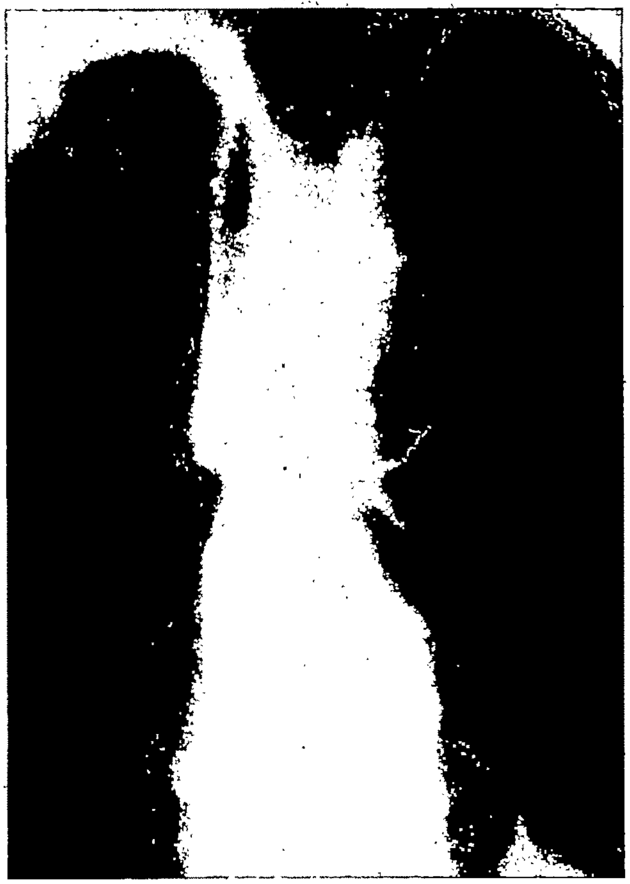

Fig 5. (Patient 5.) Tomographic view of the trachea showing the normal size of the tracheal anastomosis at day 30.

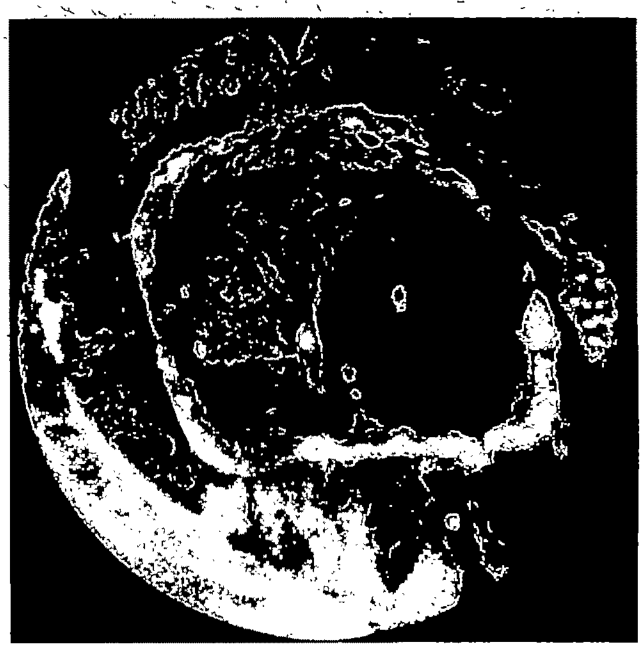

Fig 6. (Patient 6.) Endoscopic view showing good tracheal healing, grade I (15th postoperative day), related to good patency of the graft.

Comment

Revascularization of bronchial arteries in double-lung transplantation has thus been proven possible in humans. Revascularization by indirect aortic reimplantation using a saphenous vein graft is easy to perform and quite effective, allowing primary tracheal healing.

The thoracic approach may either be a median sternotomy, as in the first 3 patients, or bilateral transverse thoracotomy, as in the last patients. The trachea and the carina are approached in the mediastinal space between the ascending aorta and the vena cava through a vertical pretracheal incision of the posterior pericardial sheet. This approach makes possible an easy excision of the carina and the origin of the main bronchi after bilateral pneumonectomy. The tracheal anastomosis is performed through the same route, which avoids problems of denervation and torsion of the heart.

The duration of the operation is moderately lengthened (average ischemic time, 243 minutes). Individualization of the bronchial artery orifices and of the aortic button takes about 1 hour. However, time is spared during airway reconstitution as one needs a single tracheal instead of two bronchial anastomoses. So, in comparison with the conventional double-lung transplant technique, this double procedure adds 30 to 40 minutes. The total double-lung ischemic time is far shorter than the ischemic time of the second lung when a sequential double-lung procedure is performed, and the recipient heart ischemic time does not exceed 1 hour even when the proximal anastomosis of the venous graft is completed before the release of the aortic cross-clamp.

The results of direct revascularization, appreciated by the quality of tracheobronchial healing as assessed by bronchoscopy, are undoubtedly excellent. In this series,

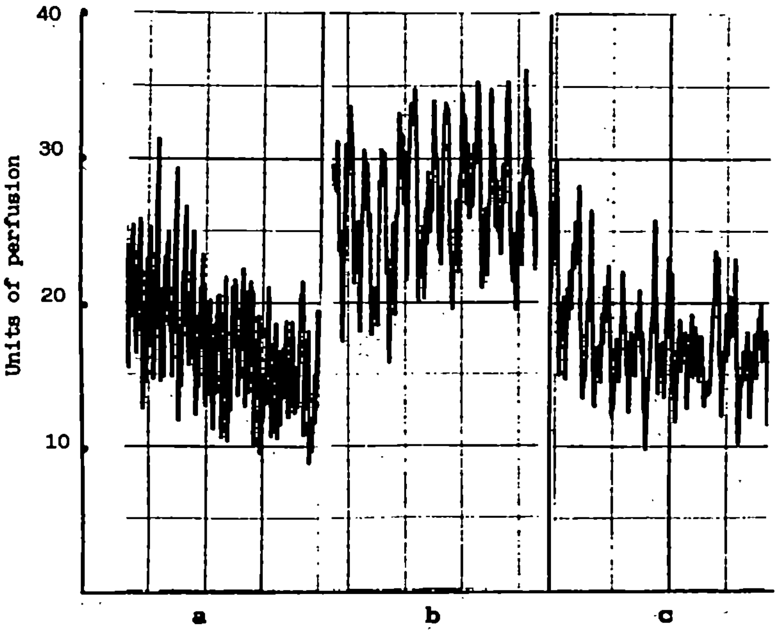

Fig 7. (Patient 8.) Laser Doppler velocimetry (day 8) showing adequate mucosal blood flow of both main bronchi in comparison with the recipient trachea's: (a) recipient trachea, (b) proximal right main bronchus, (c) proximal left main bronchus.

there was no ischemic necrosis seen, whereas this was observed in more than 40% of cases in the initial series of Patterson and associates [2]. Often, as soon as on the 15th day and universally on the 30th day, anastomotic healing was perfectly achieved with excellent epithelialization and without any luminal size reduction. Results appear to be stable at 6 months. In terms of graft patency, results are more questionable as in 2 patients, the graft was occluded at angiography on the 15th day. In the first patient, the onset of this occlusion could be suspected to have occurred on the 7th day as suggested by bronchoscopic findings, but its potential deleterious effects seem to have been overcome with the help of already well-organized adhesions and neovascularization from the wrapping tissues. Routine follow-up of graft patency with angiography may carry some risk. It implies discontinuation of anticoagulation, and this may contribute to graft thrombosis. To avoid this invasive investigation, it is now easier and safer to evaluate the efficacy of revascularization by studying the bronchial healing endoscopically, or possibly the mucosal blood flow at and around the anastomosis by laser Doppler velocimetry according to the method described in animal experiments by Inui and colleagues [12].

As far as the use of anticoagulation is concerned, it is possible that this policy reduces the incidence of graft thrombosis in view of its limited run-off into bronchial arteries and of the discrepancy between graft size and the smaller RICBA. This anticoagulation, which is started 1 or 2 days after transplantation, could induce anticoagulant-related hemorrhage, particularly in recipients who have dense pleural adhesions. Nevertheless, the two instances of pleural bleeding observed in this series were not related to the technique of revascularization or to the anticoagulation as they were dependent on pleural symphyses difficult to control through the operative approach and they occurred in the first postoperative day before the anticoagulant therapy was initiated.

Maintaining long-term anticoagulation is probably unnecessary as it appears that revascularization is most useful during the first 15 days. It is, however, certainly defendable to maintain the same anticoagulant therapy in these patients as it is practiced in patients with coronary artery bypass grafts with poor run-offs.

It is impossible to tell yet if restoration of the bronchial circulation might have some impact on development of bronchiolitis obliterans. Nevertheless, the hypothesis remains a point of interest for the future.

In conclusion, tracheobronchial revascularization to improve tracheal or bronchial healing of airway anastomoses appears to be quite logical. Compared with other experimental cumbersome techniques proposed, reimplantation of tracheobronchial arteries using a saphenous vein graft is easy, safe, original, and efficient and could be systematically recommended as an addition to double-lung transplantation. In the current practice of our transplant group, this new technique has reestablished indications for double-lung transplantation, which we had stopped doing in view of its incidence of airway complications, the incidence of such problems being up until recently much lower in heart-lung transplantation. Bronchial revascularization improves results of double-lung transplantation and, in addition, allows the use of the donor's heart in a second recipient, thus increasing the pool of donor hearts.

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Comparison Between Resected and Irradiated Small Cell Lung Cancer in Patients in Stages I Through IIIa

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The survival and recurrence of 37 patients with small cell lung cancer who underwent surgical resection were compared with those of 32 patients who were excluded from surgical resection but received radiotherapy. All but 2 patients received chemotherapy. The number of patients in the resected and nonresected groups in each pretreatment clinical stage were, respectively, as follows: 13 and 2 in stage I, 12 and 7 in stage II, and 12 and 23 in stage IIIa. The main reasons for exclusion from surgical resection were locally advanced disease in 15 patients, avoidance of pneumonectomy in 7, and poor pulmonary function in 5. In stage II, the mean tumor size was larger and there were fewer patients with peripheral tumors in the nonresected group than in the resected group. In stage IIIa, there were significantly more patients with overt N2 disease and central tumors in the nonresected group than in the resected group. The 5-year survival rate of the resected group in stage I was 67.7%. Although the nonresected group in stages II and IIIa had many adverse prognostic factors, there was no statistically significant difference between the survival of the resected and the nonresected groups. With respect to the site of first recurrence, a similar pattern was observed in the two groups in each stage, whereas local disease in stage I was completely controlled by surgical resection. These observations suggest that surgical resection can be considered a modality of treatment in clinical stage I. However, the treatment role of surgical resection in clinical stages II and IIIa, even in selected patients, remains unclear.

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The British Medical Research Council Study compared surgical therapy with radiotherapy in patients with potentially resectable small cell lung cancer (SCLC) and concluded that surgical therapy for SCLC should be abandoned [1]. Some reports supported this conclusion because there were no long-term survivors after resection [2, 3]. Therefore, surgical therapy in this disease fell into disrepute. Nonetheless, some centers, including ours, have continued to operate on patients with SCLC and have reported 5-year survival rates of 25% to 36% [4–8]. Some retrospective studies, based on a large number of SCLC patients, have also shown that the majority of long-term survivors received surgical resection [9, 10]. However, it can be thought that patients who underwent surgical resection were highly selected. To our knowledge, there is little information about the survival and recurrent patterns of patients with limited disease who were excluded from surgical resection by treatment teams that try to operate on patients with SCLC. Because of this, in the present study, we compared the survival and recurrence of patients in each pretreatment clinical stage who underwent resection with those of patients who were excluded from surgical resection but received full-dose radiotherapy.

Material and Methods

Subjects

One hundred eighty-three patients with SCLC who were cytologically or histologically diagnosed were treated in the period from 1974 to 1989 at the National Kyushu Cancer Center. There were 80 patients in pretreatment clinical stages I through IIIa. Out of these patients, 11 patients either rejected treatment or were only able to receive doses of less than 30 Gy of radiotherapy owing to progress of the disease. The subjects in this study, excluding the latter 11 patients, were 69 patients in pretreatment clinical stages I, II, and IIIa: 37 patients underwent surgical resection and 32 received full-dose radiotherapy. The staging was determined by means of physical examination; chest roentgenography; conventional tomography of the primary site, hilar, and mediastinum; bronchoscopy, and bone marrow aspiration. From 1974 to 1980, radionuclide scanning (bone, brain, liver) was done to detect occult metastases in the majority of patients. From 1981, computed tomographic scans of brain and abdomen, combined with bone radionuclide scans, were used in the majority of patients. After these patients' pretreatment staging was reviewed, restaging was done according to the new international staging system [11].

In parallel with review of the patients' records, the primary tumor size was measured on films of chest roentgenography and tomography. The longest perpendicular diameters of tumor were measured, and the prod-

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uct of the lengths was defined as tumor size. The location of the primary tumor was classified as follows: (1) peripheral tumor—the localized tumor was surrounded with normal pulmonary parenchymal tissue, (2) central tumor—the tumor was apparently located in the hilum on roentgenography or could be detected in the lobar or segmental bronchus by bronchoscopy, and (3) intermediate tumor—the tumor was located near the hilum and was connected to it by metastasized lymph nodes. Neither mediastinoscopy nor mediastinostomy was used to determine N2 disease. When N2 disease could be detected on films of chest roentogenography and tomography, it was referred to as overt N2 disease.

Treatment

In the selection of treatment modality, surgical resection was generally abandoned if the tumor, diagnosed as SCLC, required pneumonectomy for complete resection. All patients who were excluded from surgical resection received radiotherapy. Local radiotherapy in the nonresected group was given in doses from 50.2 to 75.0 Gy, the mean (± standard deviation) of which was 57.8 ± 6.1 Gy. All but 1 patient in each group received chemotherapy. In early trials, a VCMC (vincristine, cyclophosphamide, mitomycin C, and chromomycin A3) regimen was mainly used. In recent trials, regimens including CAV (cyclophosphamide, adriamycin, and vincristine), EP (etoposide and cisplatin), or other combinations using CAV or EP were mainly used. The drug dosage and schedule of these regimens have been described in detail [12]. For convenience sake, treatment with regimens like VCMC and those including CAV or EP was referred to as mild and intensive chemotherapy, respectively, in this study. Definitions of response used the standard criteria [13] for complete response, partial response, no change, and progressive disease. No patients received prophylactic cranial irradiation.

Patients were followed up at our outpatient clinic every 2 months for the first 2 years, and then every 3 or 4 months. Of these, only a few patients routinely received screening examinations by computed tomography or radionuclide scans once or twice per year after treatment to determine the presence of metastases. The majority of patients underwent computed tomography or radionuclide scans only when symptoms related to metastases appeared.

Survival rates were calculated from the start of treatment using the method of Kaplan and Meier, and statistical comparison of these was done using the two-tailed log-rank test. Differences between proportions were evaluated using the χ^2 or Student's t tests. The statistical difference was considered insignificant when the p value exceeded 0.05.

Table 1. Pretreatment Clinical Stage I

Variable	Resected Group (n = 13)	Nonresected Group (n = 2)
Age (y)	64.0 ± 8.6[a] (43–75)	60, 80
Male/female	9/4	1/1
PS 0–1	13	2
Tumor size (cm^2)	18.0 ± 5.3[b] (1–72)	12.0
Location		
Peripheral	11 (85%)	1 (50%)
Intermediate	0	0
Central	2 (15%)	1 (50%)
Bronchoscopic findings (+)	2/13 (15%)	0/1
Preoperative diagnosis	8/13 (62%)	
Chemotherapy		
Mild	6 (46%)	2 (100%)
Intensive	7 (54%)	0

[a] Mean ± standard deviation. [b] Mean ± standard error of primary tumor size in 12 patients.

PS = performance status of the Eastern Cooperative Oncology Group scale.

Results

Stage I

Patient characteristics in pretreatment clinical stage I are shown in Table 1. In the resected group, the mean tumor size of 12 primary tumors was 18.0 cm^2, ranging from 1.0 cm^2 (1 × 1 cm) to 72 cm^2 (9 × 8 cm). A small tumor located at B6 in the left lower lobe in 1 patient could not be measured. There were three T1 and ten T2 tumors. All patients underwent lobectomy.

In the nonresected group, 1 patient showed atelectasis of the right upper lobe and the other had a tumor (4 × 3 cm) in the left upper lobe. Therefore, both tumors were classified as T2. The reason for exclusion from surgical resection was unknown in the former and poor pulmonary function in the latter patient. Both patients concurrently received radiotherapy (60 and 70.2 Gy) and a single cycle of mild chemotherapy, and achieved complete response.

Survival curves are shown in Figure 1. The 5-year survival rate in the resected group was 67.7%. In the resected group, 7 patients have survived more than 60 months. As of October 1990, they are free from disease and alive 91, 95, 107, 114, 157, 163, and 177 months after

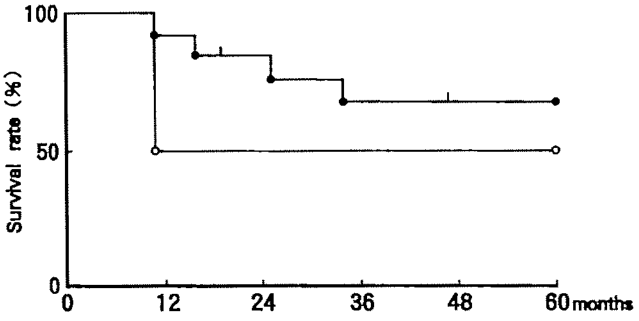

Fig 1. Survival curves of clinical stage I patients in the resected (●; n = 13) and nonresected (○; n = 2) groups. The difference between groups is not significant (p = 0.5005; χ^2 = 0.4539).

Table 2. Site of First Recurrence in Stage I Patients[a]

Site	Resected Group	Nonresected Group
Local	0	0
Distant	5 (9, 13, 15, 23, 30)	0

[a] Numbers in parenthesis indicate the time to recurrence (months) after start of treatment.

the start of treatment. In the nonresected group, the patient who had atelectasis before treatment survived for 140 months before dying of colon cancer. The cause of death and existence of recurrence in the other patient were unknown. All of the sites of first recurrence were distant (Table 2). One patient showed a nodule in the contralateral lung 30 months after initial treatment. Although the nodule could not be histologically confirmed as recurrent SCLC, it disappeared with treatment by CAV chemotherapy in 6 cycles. Therefore, this patient was included in the recurrent cases. Four patients who died of recurrence in the resected group had no local recurrence during observation.

Stage II

Table 3 shows patient characteristics in pretreatment clinical stage II. In the resected group, the mean tumor size of 11 primary tumors was 14.3 cm^2, ranging from 3.1 cm^2 (1.8 × 1.7 cm) to 33.0 cm^2 (6.0 × 5.5 cm). One tumor could not be measured due to segmental atelectasis. There were 3 T1 and 9 T2 tumors. Of 7 patients who had positive bronchoscopic findings, 4 had lesions related to hilar lymph node involvement. Lobectomy, bilobectomy, and pneumonectomy were performed in 7, 3, and 2 patients, respectively. Two operations resulted in incomplete resection due to fixed lymph node metastases.

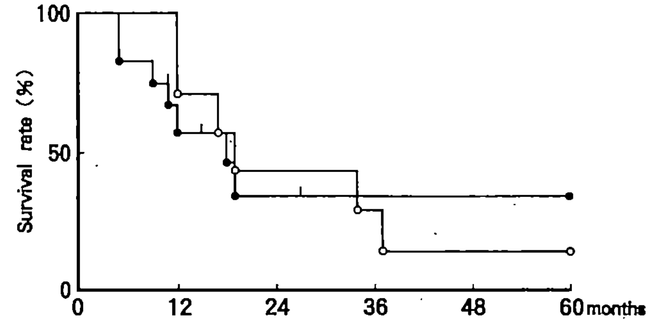

Fig 2. Survival curves of clinical stage II patients in the resected (●; n = 12) and nonresected (○; n = 7) groups. The difference between groups is not significant (p = 0.9420; χ^2 = 0.0053).

In the nonresected group, the mean tumor size of 6 measurable primary tumors was 25.4 cm^2, ranging from 10.5 cm^2 (3.5 × 3.0 cm) to 48 cm^2 (8.0 × 6.0 cm). One patient showed atelectasis of the middle lobe. All of the tumors were defined as T2. The tumor size in this group had a tendency to be larger than that in the resected group (see Table 3). Reasons for nonresection were as follows: poor pulmonary function in 2 patients, avoidance of pneumonectomy in 2, locally advanced tumor in 1, refusal of operation in 1 and unknown in 1. Four and 3 patients achieved complete response and partial response, respectively.

The resected and nonresected groups had a median survival time of 17.5 and 18.5 months and 5-year survivals of 34.3% and 14.3%, respectively (Fig 2). There was no significant difference in survival between these two groups (p = 0.9420). In the resected group, there were 2

Table 3. Pretreatment Clinical Stage II

Variable	Resected Group (n = 12)	Nonresected Group (n = 7)
Age	64.4 ± 9.4^{a} (44–76)^{b}	67.9 ± 7.2^{a} (55–77)^{b}
Male/female	8/4	5/2
PS 0–1	12	7
Tumor size^{c} (cm^2)	14.3 ± 2.5^{d} (3.1–33.0)^{b}	25.4 ± 5.7^{d} (10.5–48.0)^{b}
Location^{c}		
Peripheral	7 (58%)	1 (14%)
Intermediate	4 (33%)	4 (57%)
Central	1 (8%)	2 (29%)
Bronchoscope findings (+)	7/11 (64%)	4/7 (57%)
Preoperative diagnosis	8/12 (67%)	
Chemotherapy		
None	1 (8%)	1 (14%)
Mild	5 (42%)	5 (71%)
Intensive	6 (50%)	1 (14%)

[a] Mean ± standard deviation. [b] Range. [c] $p < 0.1$ between groups. [d] Mean ± standard error of primary tumor size in 11 and 6 patients in the resected and nonresected groups, respectively.

PS = performance status of the Eastern Cooperative Oncology Group scale.

Table 4. Site of First Recurrence in Stage II Patients[a]

Site	Resected Group	Nonresected Group
Local	3 (7, 8[b], 11)	2 (12[c], 25[c])
Distant	3 (4, 9, 37)	3 (7[c], 8, 15)

[a] Numbers in parentheses indicate the time to recurrence (months) after start of treatment. [b] Patient with incomplete resection. [c] Patients with partial response.

patients who survived more than 60 months. One has been free from disease for 71 months. The other died of recurrent disease 95 months after treatment. In the nonresected group, 1 patient treated with radiotherapy only was disease free and alive 184 months after the start of treatment, as of December 1989. Another patient was disease free for 34 months after treatment and died of respiratory failure. Table 4 shows the situation and time of appearance of first recurrence in all but 1 patient. The latter patient, who underwent incomplete resection, lacked sufficient information about site of recurrence. The patterns of the sites of first recurrence were similar to each other.

Stage III

Patient characteristics in pretreatment clinical stage IIIa are shown in Table 5. In the resected group, the mean tumor size of the 12 primary tumors was 27.7 cm^2, ranging from 5.0 cm^2 (2.5 × 2.0 cm) to 88.3 cm^2 (9.7 × 9.1 cm). Pretreatment clinical TNM stages were as follows: T3 N0 in 2 patients, T3 N1 in 1, T1 N2 in 3, and T2 N2 in 6. Lobectomy, bilobectomy, and pneumonectomy were performed in 8, 2, and 2 patients, respectively. Operation in 1 and 2 patients resulted in incomplete resection because of pleural dissemination and fixed lymph node metastases, respectively.

In the nonresected group, the mean tumor size of 14 measurable primary tumors was 18.6 cm^2, ranging from 1.6 cm^2 (1.3 × 1.2 cm) to 48 cm^2 (8.0 × 6.0 cm). Nine patients showed lobar atelectasis. Pretreatment clinical TNM staging was as follows: T3 N1 in 1 patient, T1 N2 in 2, T2 N2 in 14, and T3 N2 in 6. Because the majority of patients had locally advanced disease, there were significantly more patients with overt N2 disease and central tumors than in the resected group (see Table 5). The reasons for nonresection were as follows: locally advanced disease in 14 patients, avoidance of pneumonectomy in 5, poor pulmonary function in 2, and unknown in 2. Eleven, 9, and 3 patients achieved complete response, partial response, and no change or progressive disease, respectively.

The resected and nonresected groups had a median survival time of 31 and 17 months and a 5-year survival rate of 15.6% and 4.1%, respectively (Fig 3). Although the survival in the resected group appeared to be superior to that of the nonresected group, there was no significant difference between these two groups ($p = 0.0534$). Furthermore, when the survival curve of 5 patients in whom surgical resection was avoided as pneumonectomy was necessary for complete resection was compared with that of the resected group, the former was very similar to the latter ($p = 0.4397$). In the resected group, 1 patient has been free from disease for 63 months. In the nonresected group, 1 patient, who had brain recurrence that was treated with cranial irradiation, died of pneumonia 89 months after initial treatment. Autopsy of the latter patient found no SCLC lesion. The sites of first recurrence in the resected and nonresected groups, excluding 3 patients

Table 5. Pretreatment Clinical Stage IIIa

Variable	Resected Group (n = 12)	Nonresected Group (n = 23)
Age	65.1 ± 7.7[a] (47–75)[b]	60.5 ± 7.5[a] (48–75)[b]
Male/Female	12/0	18/5
PS 0–1	12	20
Tumor size (cm^2)	27.7 ± 7.5[c] (5.0–88.3)[b]	18.6 ± 3.5[c] (1.6–48)[b]
Overt N2 disease[d]	3/12 (25%)	18/23 (78%)
Location[e]		
Peripheral	7 (58%)	6 (26%)
Intermediate	4 (33%)	4 (17%)
Central	1 (8%)	13 (57%)
Bronchoscope findings (+)	6/11 (55%)	17/21 (81%)
Preoperative diagnosis	7/12 (58%)	
Chemotherapy[f]		
Mild	2 (17%)	13 (57%)
Intensive	10 (83%)	10 (43%)

[a] Mean ± standard deviation. [b] Range. [c] Mean ± standard error of primary tumor size in 12 and 14 patients in the resected and nonresected groups, respectively. [d] $p < 0.01$ between groups. [e] $p < 0.025$ between groups. [f] $p < 0.1$ between groups.

PS = performance status of the Eastern Cooperative Oncology Group scale.

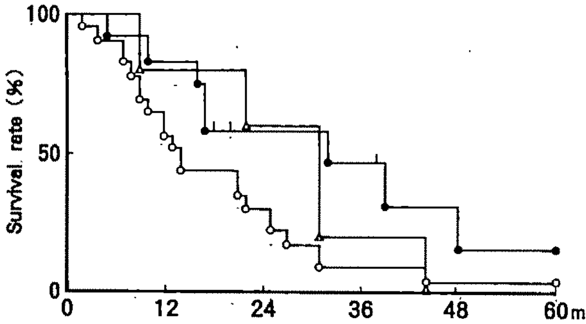

Fig 3. Survival curves of clinical stage IIIa patients in the resected (●; n = 12) and nonresected (O; n = 23) groups. The difference between groups is not significant (p = 0.0534; χ^2 = 3.7325). The survival curve of 5 patients in the nonresected group, in whom surgical resection was avoided as pneumonectomy was necessary for complete resection, is illustrated by (△). The difference between the resected and the latter groups is not significant (p = 0.4397; χ^2 = 0.6182).

with no change or progressive disease, are shown in Table 6. Of 20 patients in the latter group, there were 17 patients who had records of the site of first recurrence. Patterns of sites of first recurrence and time were similar to each other. The main sites of distant recurrence in both groups were brain in 7 patients, lung in 7, and bone in 3.

Comment

Surgical management of SCLC was largely discontinued in the 1970s, primarily because studies conducted in England showed that only 6% of patients undergoing complete resection survived beyond 2 years [1]. The Veterans Administration-Armed Forces Cooperative Study first disputed the nonoperability of SCLC [4]. It showed that 36% of patients with surgically resected asymptomatic peripheral lung nodules of SCLC survived 5 years, even though none of these patients received chemotherapy. However, in this study only 11 of the 309 patients with neoplastic peripheral nodules had SCLC.

It was not until the early 1980s that additional surgical trials confirmed the potential for long-term survival in patients with resected SCLC. In the largest of these trials, performed by the Veterans Administration Surgical Oncology Group, 148 patients with SCLC who underwent potentially curative resection were randomized to one of four prospective trials of adjuvant chemotherapy [6]. Excluding 16 patients who died postoperatively, the 5-year survival rate was 23%. The 5-year survival rate allocated by pathological TNM staging was 59.5% for T1 N0 M0, 27.9% for T2 N0 M0, and 31.3% for T1 N1 M0. Therefore, they concluded that resection is definitely indicated in patients with T1 N0 M0 lesions and probably indicated in those with T1 N1 or T2 N0 M0.

Shepherd and associates [14] recently reported the survival of patients postoperatively administered up-to-date chemotherapeutic regimens such as cyclophosphamide, doxorubicin, and vincristine or VP-16 and cisplatin. The projected 5-year survival in 63 patients was 31%. Patients in pathological stage I had a median survival of 191 weeks and a projected 5-year survival of 48%. Patients in stages II and III had median survivals of 72 and 65 weeks and projected 5-year survivals of 24.5% and 24%, respectively. These data led Shepherd and associates to conclude that adjuvant chemotherapy after operation prolongs survival and cures a significant number of patients in pathological stage I. Thus, the potential for long-term survival in resected SCLC patients was confirmed. However, the majority of reports of surgical series used pathological staging after operation. Because of this, these data can not answer the question of which patients benefit from surgical resection before treatment.

In limited disease of SCLC, survival of surgical series generally seems to be better than that in trials using standard chemotherapy and radiotherapy. However, it is presumed that surgical series represent a select subgroup within limited disease from which patients with adverse prognostic factors, such as poor general condition, supraclavicular adenopathy, pleural effusion, or locally advanced disease, have been specifically excluded. Therefore, survival of surgical series should not be compared directly with trials of nonsurgical series. There are a few reports comparing survival of patients undergoing operation with that of patients not receiving operation in the same trial. Friess and co-workers [10] have reported the median survivals of 15 patients who underwent operation and of 33 unresected patients who had similar initial presentation (eg, tumor size, performance status) to that of resected patients. Although these patients received the same treatment in the Southwest Oncology Group Study 7628, the median survival time in the resected patients was significantly prolonged compared with the nonresected patients (25 months versus 10 months). A University of Toronto Lung Oncology Group has reported the survival of 38 resected and 19 nonresected patients [8]. These patients received the same standard chemotherapy. Reasons for nonresection in the 19 patients who responded to treatment and who were eligible for surgical resection were randomization to radiotherapy in 10 patients and refusal of operation in 9. The distribution of clinical stage I and combined clinical stages II and III was

Table 6. Site of First Recurrence in Stage IIIa Patients[a]

Site	Resected Group	Nonresected Group
Local	3 (4[b], 7[b], 13)	6 (9, 11, 11[c], 14, 15[c], 32)
Distant	6 (5[b], 10, 11, 13, 16, 28)	13 (5[c], 6[c], 6[c], 8, 9, 9, 10, 10, 10, 11[c], 14, 14, 16)

[a] Numbers in parentheses indicate the time to recurrence (months) after start of treatment. Two patients in the nonresected group had the local and distant recurrences at the same time. [b] Patients with incomplete resection. [c] Patients with partial response.

the same for these two groups. However, survival of the resected group was significantly superior to that of the nonresected group. The resected and nonresected patients had a median survival time of 91 and 51 weeks and projected 5-year survival of 36% and approximately 10%, respectively. These observations may suggest that surgical resection contributed to prolonged survival. However, the survival of these nonresected patients, who seem to be highly selected within limited disease, is poor compared with the "state-of-the-art" results compiled by the International Association for the Study of Lung Cancer [15]. Therefore, it is questionable whether those observations prove the contribution of surgical resection to prolonged survival.

In the present study, we attempted to clarify the role of surgical resection in the treatment of SCLC patients in each clinical stage. In clinical stage I, the 5-year survival rate in the resected group was 67.7%. Furthermore, surgical resection resulted in complete local control. Although concurrent radiotherapy and chemotherapy, which can possibly cure a number of patients in the early stage, is currently under way [16, 17], this kind of treatment has been reported to have a high mortality rate of 10% [18]. In our series, there were no postoperative deaths. In clinical stages II and III, we could find no significant difference between the survival of the resected and nonresected groups, even though the latter group had many adverse prognostic factors, such as locally advanced disease and poor pulmonary function. Although it is hard to reach firm conclusions based on the small number of patients, these observations suggest that surgical resection can be considered a modality of treatment in clinical stage I patients. However, the treatment role of surgical resection in clinical stages II and IIIa, even in selected patients, remains unclear.

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A Study on Optimal Temperature for Isolated Lung Preservation

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Fifty-two heart-lung blocks (grafts) of New Zealand white rabbits were used for determining optimal temperature in lung preservation. Grafts were inflated with room air and preserved by simple surface cooling at arbitrarily determined temperatures for 18 hours. Graft function was assessed by nonrecirculated perfusion with autologous blood. Segmented regression models between functional parameters and preservation temperature (T) were applied for determining optimal temperature. Graft ability was also assessed from the point of view of pulmonary circulation by indocyanine green dilution rate of effluent and histological distribution of carbon particles. Significant segmented regression curves and lines between parameters of effluent oxygen tension (PO_2) and wet-dry weight ratio (W/D), and T were obtained as follows: $PO_2 = 150/(1 + 3208.1[e^{-1.17T}])$, $p < 0.01$; $PO_2 = -13.8T + 222.6$, $p < 0.05$; $W/D = 5.0 + 1.5/(1 + 0.0028[e^{0.94T}])$, $p < 0.01$; $W/D = 0.075T + 4.52$, $p < 0.05$. Optimal temperature for lung preservation by topical cooling was calculated as 8° to 9°C from each intersecting point of regression equations. Analysis of regression curves suggested that the most common hypothermic ischemic injury during preservation by topical cooling is pulmonary vascular obstruction, which might be induced at temperatures lower than the critical temperature of 6° to 7° C. Indocyanine green dilution rate and histological findings supported the results of graft functional parameters.

(Ann Thorac Surg 1992;53:101–8)

Since the clinical long-term successes in lung transplantation by the Toronto group [1], the results of lung transplantation for end-stage respiratory failure have been markedly improved as evidenced by the overall survival rate of 60% from the Washington University Lung Transplant Registry [2]. However the major limitation to the application of lung transplantation is the scarcity of donors who fulfill the criteria. Prolonging ischemic time in current preservation from a range of 4 to 5 hours [3–5] to enough time for a semielective procedure has the potential to increase the number of available donor lungs. The simple, effective method is cold storage. Topical cooling [3] and flush perfusion [4, 5] are the current preservation techniques for isolated lung, and cold storage at 4°C is used in each technique. Cooper, Wang, and their colleagues [6], however, pointed out that 10°C was superior to 4°C for lung preservation according to their ex vivo rabbit lung function assessment model. Nevertheless the accurately determined optimal temperature (OT) for maximum prolongation of graft preservation is still unclear. The purpose of our study was to determine OT for lung preservation by simple surface cooling using rabbit heart-lung blocks (grafts) as described by Stuart and associates [7] and by Wang and associates [6].

Material and Methods

Fifty-two male New Zealand white rabbits, weighing 3.0 to 3.5 kg, were used for this experiment. Five of the 52 rabbits were used for control values of blood gas analysis, pulmonary artery pressure, and pulmonary wet-dry weight ratio.

Graft Harvesting and Preservation

Our method of harvesting the heart-lung block followed that of Wang and associates [6]. Sixty milliliters of autologous blood for perfusion was rapidly exsanguinated through the right atrium. The graft was then harvested and the blood was kept in a refrigerator at 4°C for 18 hours. The graft was immersed in physiological saline solution that was precooled to an arbitrarily determined temperature. The lung of the graft was inflated with room air at 15 cm H_2O of airway pressure, and the trachea was clamped. The graft was stored in another refrigerator (Incubator CR-14; Hitachi, Tokyo, Japan) at the same predetermined temperature for 18 hours.

Graft Preparation

The graft was prepared for functional assessment by the method of Wang and associates [6] as in Fig 1. The graft was rewarmed in the vapor chamber maintained at 37°C. The infusate blood was also rewarmed to 37°C.

Lung Functional Assessment

SEPARATE BILATERAL LUNG PERFUSION (20 RABBITS). Each lung of the graft was separately perfused for graft func-

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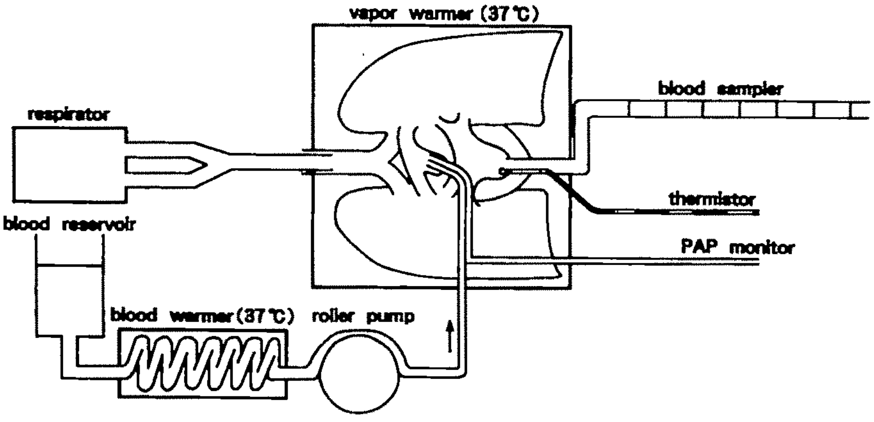

Fig 1. Schema of graft function assessment model. (1) The right lung was used for low-flow perfusion (10 mL/min) without ventilation. (2) The left lung was used for high-flow perfusion (40 mL/min) with ventilation (room air, tidal volume = 15 mL, respiratory rate = 25/min, positive end-expiratory pressure = 0.5 cm H_2O). (PAP = *pulmonary artery infusion pressure.)*

tional assessment. The right lung of the graft was used first for investigating pulmonary circulation. The left pulmonary hilus was clamped with a Bulldog vascular clamp to enable perfusion of the right lung of the graft only, while the trachea remained clamped to keep the right lung inflated. A drainage tube with a thermistor in the left ventricle was connected to a blood sampling tube (inner diameter, 5 mm; length, 60 cm; marked every 10 cm; volume of each part, 2 mL), which was kept horizontal with 5 cm H_2O of left atrial pressure. The graft was perfused by a roller pump (RP-NE3, Furue Science, Tokyo, Japan) at low flow (10 mL/min) without ventilation. Blood perfusion pressure (PAP) was monitored during perfusion. The perfusion was stopped when the sampling tube filled with blood. The tube was sealed at each 10-cm mark. The blood in each sealed section underwent blood gas analysis (ABL-3, Radiometer, Copenhagen, Denmark) and the highest oxygen tension (PO_2) in the six parts was taken.

The left lung of the graft was used to measure oxygenation capacity. A glass tube (inner diameter, 4 mm; length, 20 cm) for blood sampling was connected to the drainage tube. The right hilus was clamped and the clamps on the left hilus and the trachea were released. The ventilation of the graft with room air, a tidal volume of 15 mL, respiratory rate of 25 cycles/min, and positive end-expiratory pressure of 0.5 cm H_2O was started 5 minutes before the left lung perfusion. The graft was perfused for 1 minute at a flow rate of 40 mL/min. Blood perfusion pressure was monitored during perfusion. At the end of perfusion, the effluent blood in the glass tube was sampled for blood gas analysis.

After perfusion, the left lung wet weight was measured as described by Cooper and associates [8] and dried at 95°C for 48 hours in a drying sterilizer (Model SH-61; Yamato Scientific Co, Ltd, Tokyo, Japan) as described by Wood and More [9]. The lung wet-dry weight ratio (W/D) was then calculated.

The duration from the end of preservation to the beginning of perfusion was 30 minutes.

INDOCYANINE GREEN DILUTION RATE. Bilateral lungs of 8 grafts preserved at 4° to 14°C were perfused with blood that contained 0.25 mg of indocyanine green at a flow rate of 20 mL/min without ventilation to check pulmonary circulation. The drained blood was collected in a blood sampling tube as mentioned in the previous section. The blood in the first sealed part (initial blood) was examined for indocyanine green content by photoanalyzer (Spectrophotometer MPS2000; Shimazu Co Ltd, Kyoto, Japan). Indocyanine green content was expressed as a percentage of venous perfusate.

HISTOLOGY. Bilateral lungs of 12 grafts preserved at 4°C, 8°C, and 15°C were perfused with blood containing 1 mL of colloidal carbon black at a flow rate of 20 mL/min without ventilation to compare pulmonary circulation. The perfused graft was immersed in 10% formalin and stained with hematoxylin and eosin.

Oxygen Tension Correction

Oxygen tension of drained blood was corrected for blood temperature according to Kelman-Nunn's formula [10].

Determination of Optimal Temperature

Two segmented polynomial regression models [11] obtained by the method of least squares between graft function parameters and preservation temperature were used. Each regression equation was computed separately below and above an assumed join point. Minimum residual sum of squares was applied for selecting the point and for fitting curves. The intersecting point of the two significant curves was considered to be the optimal temperature. An *F* test was used for the significance of regression curves, and a *p* value of less than 0.05 was considered to be significant. Values were expressed as mean ± standard deviation.

Animal Care

All experimental animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Institute of Health (NIH publication No. 85-23, revised 1985).

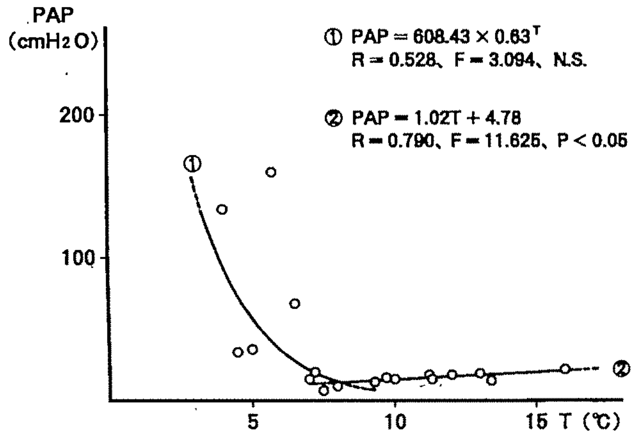

Fig 2. Regression line and curve between pulmonary artery infusion pressure (PAP) during low-flow perfusion without ventilation, and graft preservation temperature (T). (F = variance ratio; R = multiple correlation coefficient.)

Results

Seven of 52 rabbits were omitted from the study because of heart failure during harvesting or barotrauma of the lung during expansion. Blood gas analysis of the venous infusate just before perfusion gave the following results: pH, 7.28 ± 0.08; carbon dioxide tension, 38.0 ± 5.2 mm Hg; PO_2, 20.9 ± 5.5 mm Hg. The temperature of effluent blood in the left ventricle at completion of perfusion was 26.1° ± 2.1°C in all grafts tested for separate bilateral lung perfusion. Control values of blood gas analysis, PAP, and W/D ratio were as follows: pH, 7.472 ± 0.065; carbon dioxide tension, 28.8 ± 7.1 mm Hg; PO_2, 102.8 ± 23.6 mm Hg; PAP, 17.2 ± 4.0 cm H_2O; W/D, 5.3 ± 0.1.

Low-Flow Perfusion Without Ventilation

Two points each of PAP and PO_2 out of 20 grafts were omitted because of incorrect assessment procedure.

A segmented curve and line between preservation temperature (T) and PAP were obtained as follows (Fig 2): $PAP = 608.43(0.63^T)$, $R = 0.528$, $F = 3.094$, not significant; $PAP = 1.02T + 4.78$, $R = 0.790$, $F = 11.625$, $p < 0.05$. Blood perfusion pressure in the range below the point of intersection of 8.3°C increased exponentially, and perfusion of grafts preserved at 4° to 6°C was difficult.

The relationship between PO_2 and T is shown in Figure 3. A sigmoid curve with a point of inflection at 6.5°C was fitted in the range below the point of intersection of 8.2°C as follows: $PO_2 = 139.15/(1 + 224.64[e^{-0.83T}])$, $R = 0.925$, $F = 53.217$, $p < 0.01$. A negative linear correlation, which was not significant, between PO_2 and T was obtained in the range above the point of intersection as follows: $PO_2 = -4.35T + 148.23$, $R = 0.604$, $F = 5.174$, not significant. If the PO_2 of effluent was assumed to reflect alveolar PO_2, grafts preserved above the intersection maintained a PO_2 greater than 70 mm Hg. The low PO_2 of grafts preserved at 4° to 6°C suggested a shift in the alveolar level rather than oxygen consumption during preservation.

Change of indocyanine green contents according to T is shown in Figure 4. The indocyanine green content in grafts preserved at 4° to 6°C was more than 80% to 90% of that in venous perfusate, whereas that in grafts preserved at temperatures greater than 7° to 8°C remained at about 50%. The graft residual blood volume, which is considered to be 25% [12] of wet lung weight, was 3 mL. If the initial perfusate of 2 mL was assumed to be diluted with residual blood in the graft, then the indocyanine green dilution rate in initial blood is calculated as 40%. The values of grafts preserved at temperatures greater than 7° to 8°C were near the calculated rate, and effluent was well diluted with residual blood. The values of grafts stored at 4° to 6°C mean that perfusate was drained without dilu-

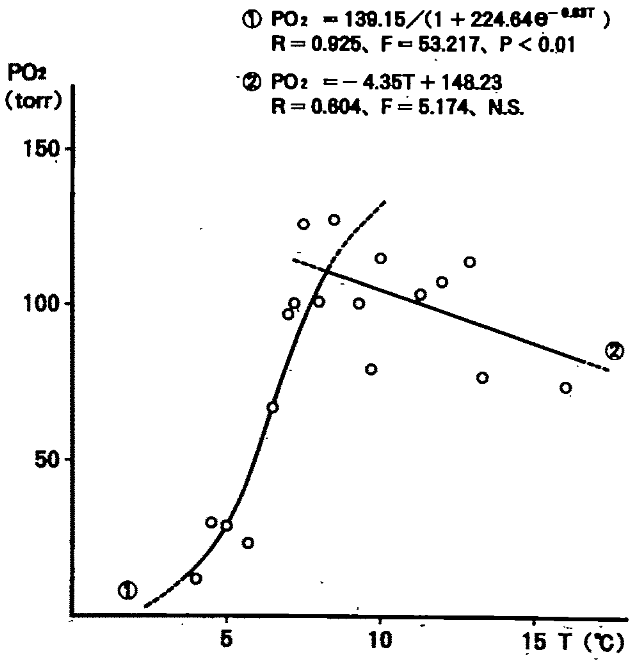

Fig 3. Regression line and curve between blood oxygen pressure (PO_2) during low-flow perfusion without ventilation and graft preservation temperature (T).

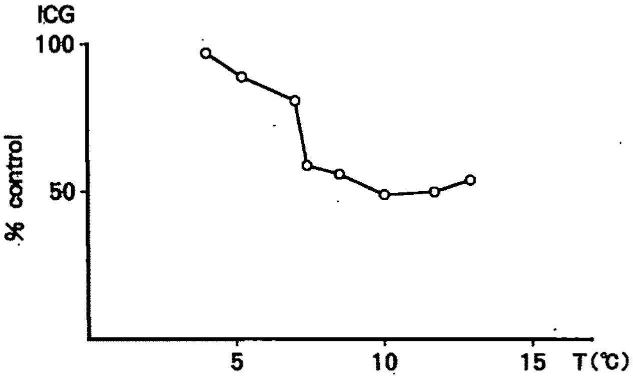

Fig 4. Change in indocyanine green (ICG) dilution rate in initially drained blood during low-flow perfusion without ventilation according to graft preservation temperature (T). Indocyanine green dilution rate was expressed as a percentage of venous perfusate.

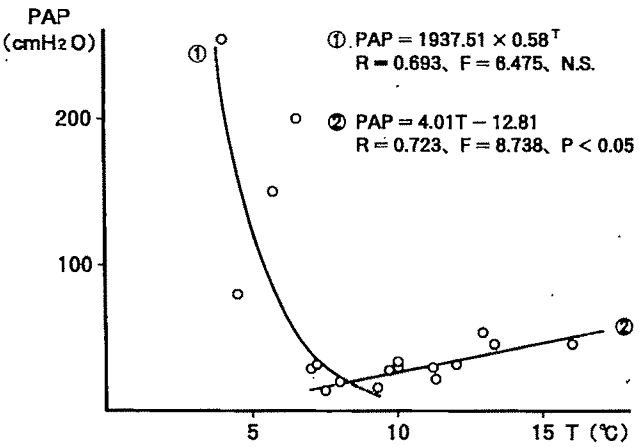

Fig 5. Regression line and curve between pulmonary artery infusion pressure (PAP) during high-flow perfusion with ventilation and graft preservation temperature (T).

tion with graft residual blood and supported the results concerning PAP and PO_2.

High-Flow Perfusion With Ventilation

Two points of PAP and one point of PO_2 out of 20 grafts were omitted because of incorrect assessment procedure.

A segmented curve and line between PAP and T were obtained as follows (Fig 5); PAP = $1937.51(0.58^T)$, $R = 0.693$, $F = 6.475$, not significant; PAP = $4.01T - 12.81$, $R = 0.723$, $F = 8.738$, $p < 0.05$. Blood perfusion pressure in the range below the point of intersection of 8.3°C increased exponentially. The pattern of PAP change was almost the same as that in nonventilated perfusion.

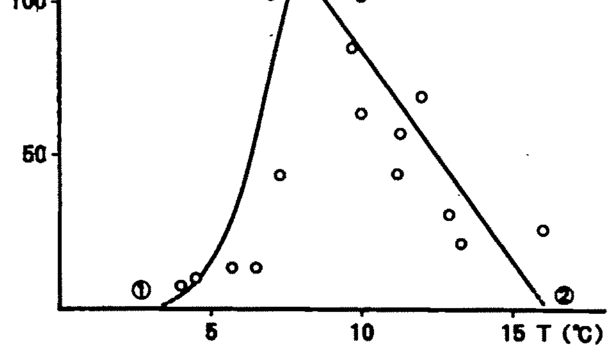

Fig 6. Regression line and curve between blood oxygen pressure (PO_2) during high-flow perfusion with ventilation and graft preservation temperature (T). Significant regression equations 1 and 2 intersected at the temperature of 7.9°C.

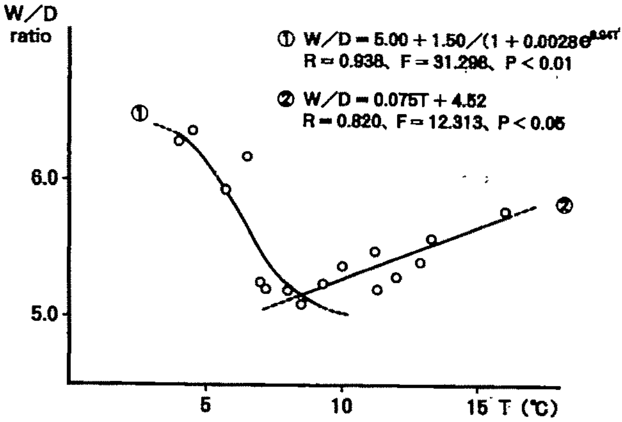

Fig 7. Regression line and curve between lung wet-dry weight ratio (W/D) during high-flow perfusion with ventilation and graft preservation temperature (T). Significant regression equations 1 and 2 intersected at the temperature of 8.6°C.

The relationship between PO_2 and T in ventilated perfusion is shown in Figure 6. A diphasic regression curve and line were obtained as follows: $PO_2 = 150.0/(1 + 3208.07[e^{-1.17T}])$, $R = 0.880$, $F = 27.510$, $p < 0.01$; $PO_2 = -13.78T + 222.60$, $R = 0.800$, $F = 14.203$, $p < 0.05$. The intersecting point of the significant segmented curve and line was 7.9°C. The sigmoid curve had a point of inflection at a temperature of 6.9°C. The oxygenation capacity was lost in grafts preserved at 4°C and 15°C on regression equations.

The relationship between W/D ratio and T is shown in Figure 7. A diphasic regression curve and line were obtained as follows: $W/D = 5.0 + 1.5/(1 + 0.0028[e^{0.94T}])$, $R = 0.938$, $F = 31.298$, $p < 0.01$; $W/D = 0.075T + 4.52$, $R = 0.820$, $F = 12.313$, $p < 0.05$. The sigmoid curve had a point of inflection at 6.3°C. The intersecting point of the significant segmented curve and line was 8.6°C.

Structural Comparison of Pulmonary Circulation

The grafts preserved at 8°C in which oxygenation capacity was best retained, and at 4°C and 15°C in which the capacity was lost on a regression curve of PO_2, were selected for structural comparison of pulmonary circulation. Typical gross and histological photographs of grafts preserved at each temperature are shown.

GROSS FINDINGS. Figure 8 shows cut surfaces of lung perfused with blood containing colloidal carbon black. The cut surface of the grafts preserved at 4°C showed massive hemorrhage in the lower lung field due to hydrostatic effect. Other regions were not stained by carbon black. The cut surface of the grafts preserved at 8°C was homogeneously stained with carbon black. In the grafts preserved at 15°C, the cut surface showed diffuse "leopard spot" lesions with accompanying bronchioles in their centers.

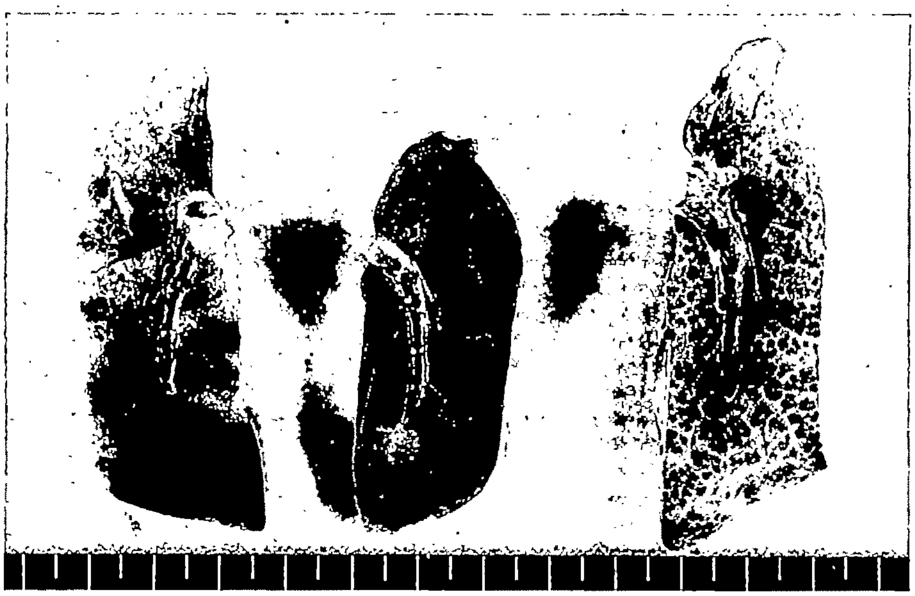

Fig 8. Cut surfaces of lungs perfused with blood containing colloidal carbon: (Left) preserved at 4°C, (Middle) preserved at 8°C, (Right) preserved at 15°C.

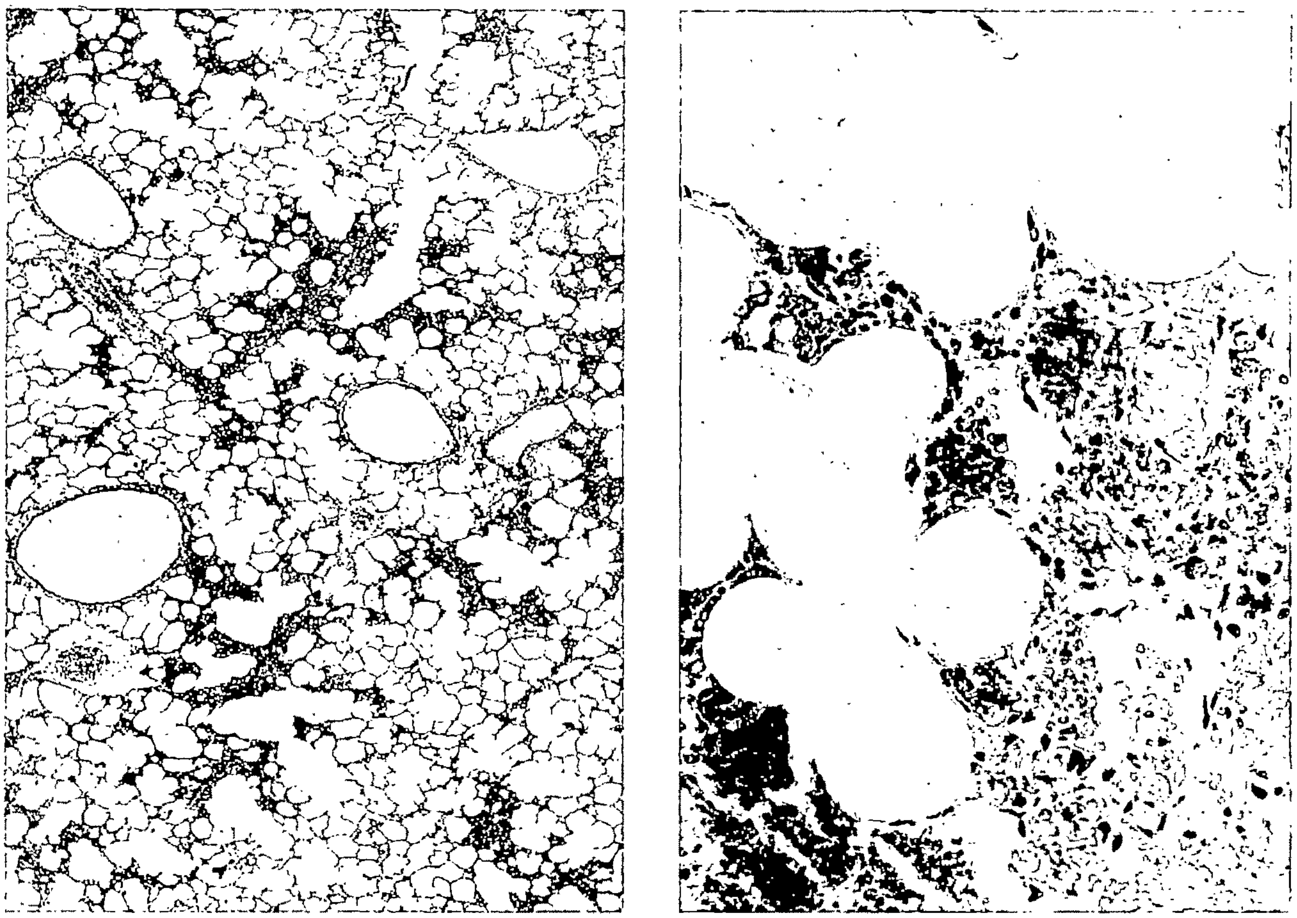

Fig 9. Histological photographs of perfused lung preserved at 4°C. (A) Pulmonary arterioles running along bronchioles were obstructed, with accompanying prominent perivascular cuffing. Hemorrhagic lesions were located around the respiratory bronchiole level. (Hematoxylin and eosin, ×40 before 4% reduction.) (B) Massive hemorrhage in alveolus. Carbon particles were not seen in capillaries but were found in macrophages. (Hematoxylin and eosin, ×400 before 5% reduction.)

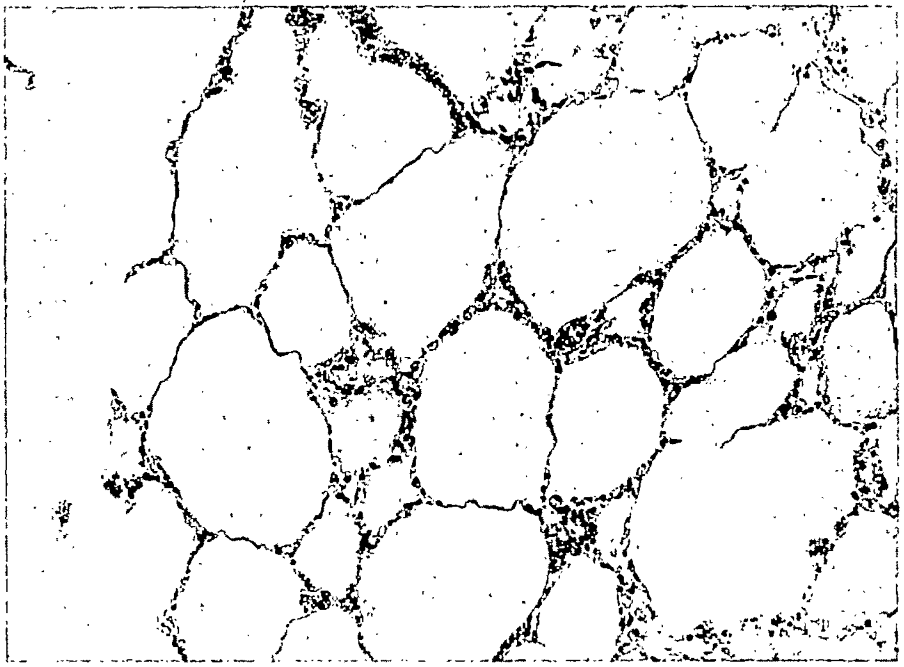

Fig 10. Histological photograph of perfused lung preserved at 8°C. Hemorrhagic lesions were not recognized. Carbon particles filled capillaries as well as arteries and veins. (Hematoxylin and eosin, ×400 before 30% reduction.)

HISTOLOGICAL FINDINGS. Figures 9A and 9B are histological photographs of a graft preserved at 4°C. In Figure 9A, pulmonary arteries with accompanying perivascular cuffing were obstructed. Focal hemorrhage was prominent around the respiratory bronchiole level. Figure 9B shows massive hemorrhage in alveolae. Carbon particles were not seen in capillaries in spite of the high perfusion pressure. Carbon particles were phagocytosed by macrophages in alveolae. Destruction in the peripheral area of the pulmonary artery was a typical finding in grafts preserved at 4°C.

Figure 10 is a photomicrograph of a graft preserved at 8°C. In this graft, hemorrhaging is not recognized. Carbon particles filled capillaries as well as pulmonary arteries and veins. Pulmonary circulation in a graft preserved at 8°C was intact.

Figures 11A and 11B are histological photographs of a graft preserved at 15°C. The "leopard spot" lesion was a lobular hemorrhage. Pulmonary arteries were not obstructed. Carbon particles, which are few in number compared with those in a graft preserved at 8°C, are recognized in capillaries. This finding suggests vascular patency is still retained at the end of the preservation.

Comment

Organs for distant procurement are preserved at 4°C according to current technique. But hypothermia has some disadvantages such as causing rigidity of cell membranes, Na^+/K^+ adenosine triphosphatase deterioration [13], and change of protein conformation [14].

There have been no systematic studies of the optimal temperature for lung preservation except for that by Wang and associates [6]. They concluded in their ex vivo rabbit experiment that preservation of lung at 10°C was superior to preservation at 4°C or 15°C. But it is still unclear whether an accurate OT is between 4°C and 10°C or between 10°C and 15°C.

Our experimental model for determining OT basically followed the method of Wang and associates, but some alterations were needed for determining OT. Autologous blood instead of homologous blood was applied for graft perfusion. Perfusion time was shortened to 1 minute because of the blood volume limitation. Pulmonary circulation, however, reached a steady state within 20 seconds in nonrecirculated perfusion, so a 1-minute perfusion was acceptable for graft functional assessment. The graft function was also assessed by separate bilateral lung perfusion to compensate for a shorter period perfusion. An inflated right lung perfusion without ventilation was used for investigation of graft pulmonary circulation. Preservation of the circulatory route is one of the most important factors for graft function, because the lung is a "leaky" organ [15]. We assumed that inflated lung perfusion without ventilation may provide a more direct assessment of graft circulatory function. This method avoids the effect of nonuniform ventilation, because the oxygen pressure in all alveolae could be assumed to be equal. The graft was inflated with room air during preservation in the manner of Wang and associates, because a deflated rabbit lung was difficult to reexpand for uniform ventilation. It is also said that the isolated lung needs aerobic metabolism [16] and the inflated lung has more ischemic tolerance [17].

Using this graft function assessment model, OT was determined as 8° to 9°C from the intersecting point of a significant segmented regression curve and line of PO_2 and W/D ratio. The similarity of join points for all functional parameters supports the appropriateness of the selection of OT, which lies within the same relatively narrow range.

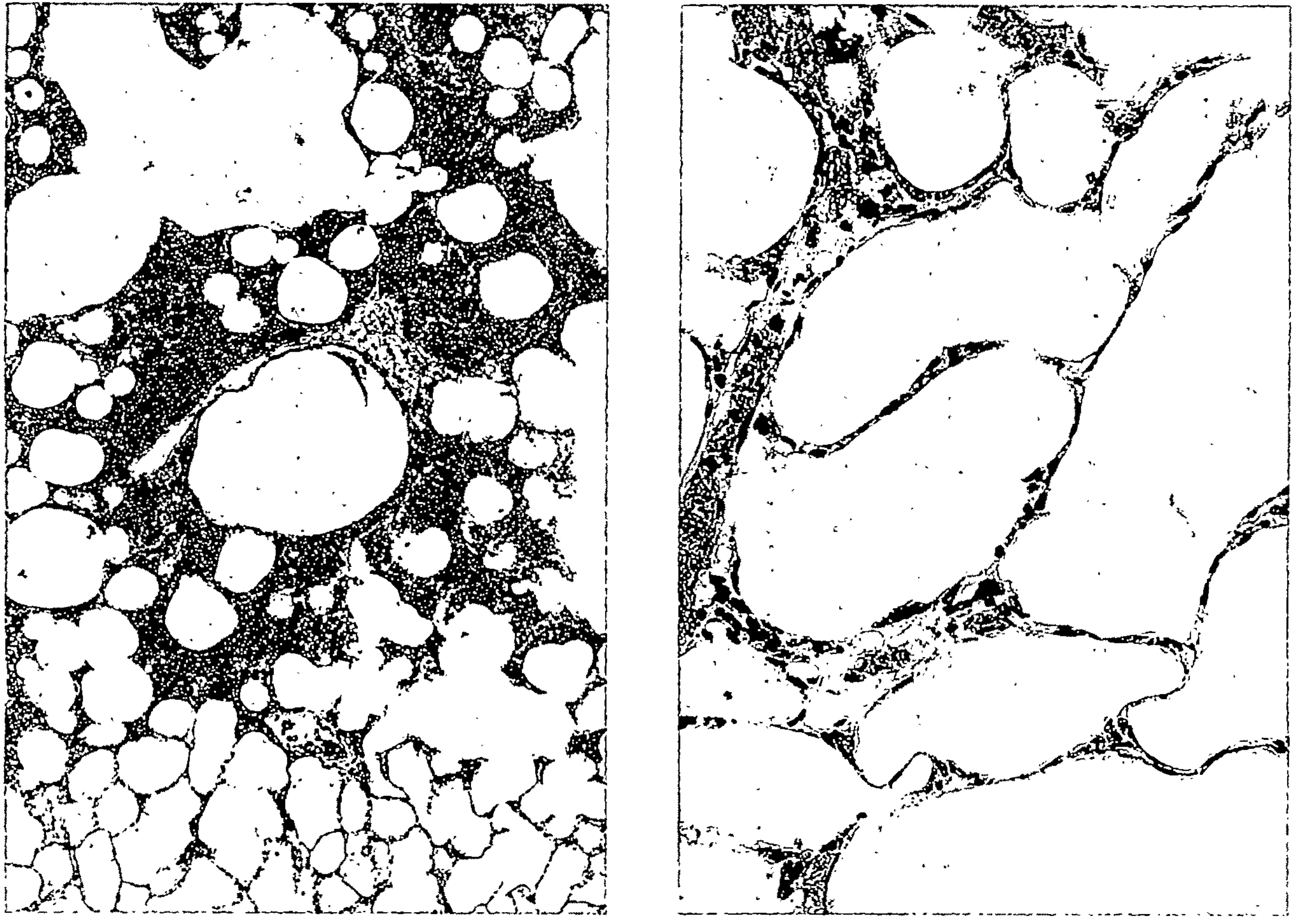

Fig 11. Histological photographs of perfused lung preserved at 15°C. (A) Arterioles running along bronchioles were not obstructed. Hemorrhaging was prominent around bronchioles in "leopard spot" lesions in macroscopic findings. (B) A few carbon particles were recognized in capillaries. (Hematoxylin and eosin, [A] ×40, [B] ×400, both before 4% reduction.)

Diphasic change of these parameters according to preservation temperature suggested two different mechanisms for graft injury during preservation. Parameters of nonventilated perfusion and indocyanine green dilution rate showed abrupt change between 4° to 6°C and 7° to 8°C. Pulmonary vascular obstruction was considered to be related to this change in the grafts preserved at lower temperatures. Each fitted sigmoid curve of PO_2 and W/D ratio in relation to the preservation temperature had a point of inflection at the range limit of 6° to 7°C. This point might be related to the critical temperature for vascular obstruction. The mechanism of this obstruction is unknown. Martin and associates [18] explained adenosine triphosphatase cold sensitivity as being responsible for hypothermic ischemic injury and said that different organs have specific temperatures for adenosine triphosphatase deterioration. The obstruction of pulmonary vessels might cause a no-reflow phenomenon [13], which has been demonstrated in the kidney [19], brain [20], and heart [21], if a graft preserved at 4° to 6°C for a long period was reimplanted. Linear change of parameters in grafts preserved at temperatures above the point of intersection might be related to warm ischemic injury in which vascular patency was kept until the end of preservation.

The use of carbon particles is a classic method for structural investigation of the circulation [20, 22]. They pass through all capillaries without leaking from intact vessels under physiological perfusion pressure. Their ease of viewing makes distribution of blood flow detectable microscopically as well as macroscopically. Microvascular destruction was classified clearly by this method. The grafts preserved at 8°C showed intact microvasculature even in histological investigation. The findings of massive hemorrhage and the lack of carbon particles in capillaries also supported the hypothesis that the deterioration of grafts preserved at 4°C is related to vascular obstruction. The findings of uniform and diffuse "leopard spot" lesions and the presence of carbon particles in capillaries supported the hypothesis that the deterioration of grafts preserved at 15°C is related to permeability injury, not vascular obstruction. These findings well explained the diphasic change of functional parameters according to preservation temperature and the different mechanisms for graft injury.

For the purpose of determining accurately the OT for lung preservation, we looked only at topical cooling, excluding other factors such as pulmonary flushing with or without vasodilator for the sake of simple analysis. The results of the OT and the microvascular change should be reconfirmed by in vivo experiments. Reliable data for the OT for topical cooling will be a good control for other preservation techniques. A question to be answered in the future is whether the OT is the same in other preservation methods such as flush technique.

In summary, our report demonstrates that the OT for lung preservation by topical cooling is 8° to 9°C and that pulmonary vascular obstruction is related to hypothermic ischemic injury.

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Selective Cerebral Perfusion During Operation for Aneurysms of the Aortic Arch: A Reassessment

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Thirty-two consecutive patients with thoracic aortic aneurysms who required aortic arch reconstruction were operated on with the aid of extracorporeal circulation and selective cerebral perfusion between January 1986 and August 1990. For selective cerebral perfusion, blood was infused into both the innominate and left common carotid arteries at a rate of 10 mL · kg^{-1} · min^{-1} using a single roller pump separately from the systemic circulation. In 9 patients treated before March 1987, the operations were performed without open aortic anastomosis (group 1), whereas in 23 patients treated from March 1987 onward we used open aortic anastomosis (group 2). The extracorporeal circulation and cardiac arrest times were significantly longer in group 2, but there was no significant difference in the cerebral perfusion time. Early death occurred in 1 patient in group 1 and 2 in group 2. No serious cerebrospinal neurological complications occurred in either group, and there were similar rates of postoperative hepatic and renal dysfunction in both groups. The present data suggest that selective cerebral perfusion and open aortic anastomosis are useful methods for thoracic aortic aneurysm operation requiring complex repair of the aortic arch.

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In the treatment of aneurysms of the thoracic aorta requiring aortic arch reconstruction, the selection of appropriate support methods to prevent cerebral ischemia is an important factor in improving the operative results. Methods for the prevention of cerebral ischemia include selective cerebral perfusion (SCP) [1–7], which has a long history, and hypothermic circulatory arrest (HCA) [8–16], which was introduced more recently. We have previously reported that both methods were useful as support procedures for preventing cerebral ischemia [17]. However, HCA is subject to limitations on the duration of cerebral circulatory arrest and, therefore, SCP must be used as the support procedure when it is anticipated that cerebral ischemia of at least 1 hour will occur. The technique of open aortic anastomosis has been used with HCA, in which the distal aortic arch is left open while the distal graft anastomosis is performed [4, 8, 9, 18].

In the present study, we investigated the results obtained in aortic arch aneurysm operations using SCP, and compared the mortality and morbidity between groups of patients with and without open aortic anastomosis.

Material and Methods

The subjects were 32 consecutive patients in whom SCP was used as a support procedure to prevent cerebral ischemia during operations for aortic arch aneurysms in the period between January 1986 and August 1990. Eleven patients with aortic arch aneurysms in whom HCA was used during operation were excluded. The subjects ranged in age from 24 to 80 years, with a mean age (± standard deviation) of 60 ± 12 years. There were 20 men and 12 women. The aneurysm was a Stanford type A aortic dissection in 23 patients, including 7 with acute dissection who were seen within 2 weeks of onset. Among these 23 patients, aortic arch dissection with a primary intimal tear in the aortic arch was found in 12, and rupture into the pericardial or left pleural cavities occurred in 3 of these 12 patients. In another 10 patients, the intimal tear extended throughout the aortic arch, and in 1 there was compression of the arch vessels. The aneurysm was secondary to arteriosclerosis in 9 patients. Regarding associated diseases, aortic regurgitation was present in 12 patients (including 5 with annuloaortic ectasia), coronary artery disease in 3, and classic Marfan's syndrome in 3. Four of the 32 patients (12.5%) had undergone previous cardiovascular operations, and 9 patients (28.1%) underwent emergency operations within 24 hours after hospitalization because of frank or impending aneurysmal rupture.

All operations were performed using extracorporeal circulation, with the arterial return cannula being placed in a femoral artery and a single two-stage cannula for venous drainage being positioned in the right atrium. The left side of the heart was vented through the right superior pulmonary vein. Extracorporeal circulation was instituted and the ascending aorta was cross-clamped when the body temperature began to decrease. Myocardial protection was provided with cold blood cardioplegia and topical cooling. The technique of cannulation and the method of selective cerebral perfusion have been described previously [17]. When the rectal temperature reached 25°C, the innominate artery (IA), left common carotid artery (LCCA), and left subclavian artery (LSA)

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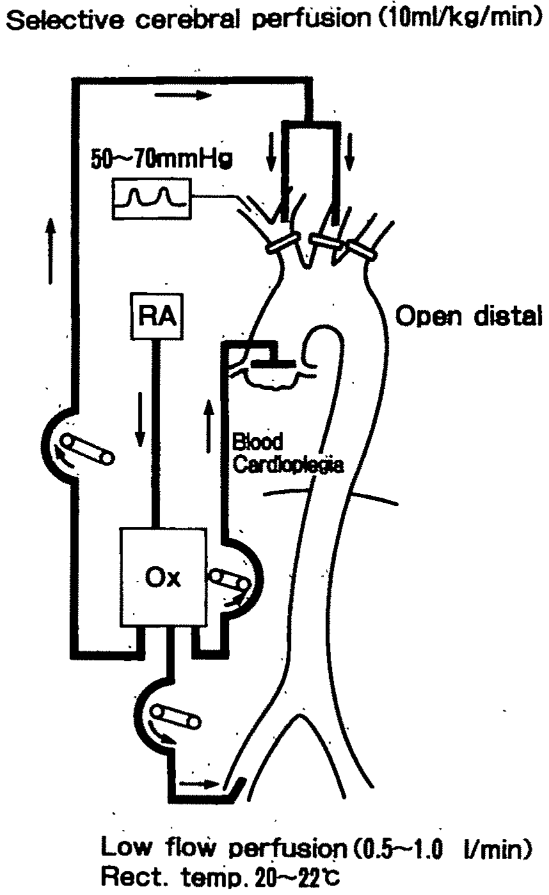
Selective cerebral perfusion (10ml/kg/min)
50~70mmHg
RA
Open distal
Blood Cardioplegia
Ox
Low flow perfusion (0.5~1.0 l/min)
Rect. temp. 20~22℃

Fig 1. System used for preventing cerebral ischemia during operations on aortic arch aneurysms. (Ox = oxygenator; RA = right atrium.)

were cross-clamped. Blood was then perfused into both the IA and the LCCA using a single roller pump separated from the systemic circulation (Fig 1). A total volume of 10 mL · kg^{-1} · min^{-1} was supplied to these vessels, and thus to both carotid arteries and the right subclavian artery. The right radial arterial pressure was adjusted to between 50 and 70 mm Hg to regulate the perfusion pressure.

The subjects were divided into two groups, ie, those undergoing and not undergoing open aortic anastomosis. Group 1 consisted of 9 patients treated before March 1987 in whom the distal end of the aortic arch was cross-clamped and high-flow perfusion was performed through the femoral artery at a rate of 40 mL · kg^{-1} · min^{-1}. Group 2 consisted of 23 patients treated from March 1987 onward in whom open aortic anastomosis was used. When the rectal temperature reached 22°C, the distal side of the aortic arch was opened, and low-flow perfusion was performed through the femoral artery at a rate of 0.5 to 1.0 L/min. Blood was aspirated from the operative field with a sucker and was returned to the cardiopulmonary bypass circuit. While the aortic arch was left open, the distal graft anastomosis and arch reconstruction were performed.

Table 1 shows the preoperative clinical data for groups 1 and 2. There were no significant differences between the two groups with regard to age, sex, etiology, previous operation, and emergency operation. However, considering that patients with acute aortic dissection and associated diseases like aortic regurgitation, annuloaortic ectasia, and coronary artery disease were all included in group 2, this group obviously had the more seriously ill patients.

Woven Dacron grafts with a porosity of 50 mL were used. Preclotting of grafts was performed by immersion in a 25% albumin solution, followed by heating in an autoclave for 5 minutes at 130°C. The operation was performed through a median sternotomy alone in 3 patients in group 1 and through sternotomy together with left

Table 1. Surgical Treatment of Aneurysms of the Aortic Arch With the Aid of Selective Cerebral Perfusion

Variable	Group 1	Group 2	p Value
Period	Jan 1986–Feb 1987	Mar 1987–Aug 1990	
No. of patients	9	23	
Open aortic anastomosis	No	Yes	
Age (y)	66 ± 7	57 ± 12	NS
Sex (male/female)	7/2	13/10	NS
Etiology			
Dissecting aneurysm (type A)	5	18	NS
Acute	0	7	NS
Chronic	5	11	NS
Nondissecting aneurysm	4	5	NS
Associated disease	0	18	<0.01
AR (AAE)	0	12 (5)	<0.05
CAD	0	3	NS
Marfan's syndrome	0	3	NS
Previous operation	1	3	NS
Emergency operation	2	7	NS

AR = aortic regurgitation; AAE = annuloaortic ectasia; CAD = coronary artery disease; NS = not significant.

Table 2. Operative Technique

Operative Technique	Group 1	Group 2	p Value
Graft replacement	8	21	NS
Ascending + partial aortic arch	3	7	NS
+ACS		2	
+AVR		0	
+Bentall		2	
+CABG		2	
Ascending + total aortic arch	1	14	<0.025
+ACS		2	
+AVR		3	
+Bentall		3	
+CABG		1	
Ascending + arch + descending	4	0	<0.001
Patch angioplasty	1	2	NS
Total	9	23	

ACS = aortic cusp suspension; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; NS = not significant.

thoracotomy in the other 6 patients. In group 2, median sternotomy alone was used for all patients.

The operative techniques used are shown in Table 2. Resection of the aneurysm and Dacron graft replacement was used in all patients except 1 in group 1 and 2 in group 2 who underwent patch angioplasty of the aortic arch. Extensive graft replacement of the aorta, including the ascending aorta, the aortic arch, and the distal one third of the descending aorta, was performed more commonly in group 1 than in group 2. On the other hand, group 2 more commonly underwent graft replacement of the ascending aorta and the total aortic arch just below the origin of the LSA. Partial replacement of the aortic arch together with the ascending aorta was performed when an intimal tear was present in the vicinity of the innominate artery. The operative procedure then involved oblique resection of the aortic arch, including the intimal tear, and anastomosis with the Dacron graft including the orifices of the arch vessels.

Concomitant procedures in group 2 included aortic cusp suspension in 4 patients, aortic valve replacement in 3, Bentall's procedures using a composite graft in 5, and coronary artery bypass grafting in 3. Aortic valve repair or replacement and the distal anastomoses for coronary artery bypass grafting were always performed during cooling by extracorporeal circulation.

After extracorporeal circulation was discontinued, protamine sulfate, fresh frozen plasma, and platelets were administered to maintain normal blood coagulability and minimize oozing from the graft.

Data are expressed as the mean ± standard deviation. For statistical analysis, Student's t test or the χ^2 test were used, and significant differences were defined as p less than 0.05.

Results

Early death occurred within 1 month postoperatively in 3 patients (9.4%): 1 in group 1 (11.1%) and 2 in group 2 (8.7%). No significant difference was seen between the two groups in the early mortality rate (Table 3).

One patient in group 1, who had previously undergone patch angioplasty of the ascending aorta for an acute type A dissection, was treated by extensive graft replacement of the ascending aorta, the aortic arch, and the distal one third of the descending aorta for an aneurysm of the distal false lumen. This patient subsequently died of multiple organ failure associated with hemorrhage.

One patient in group 2 who was on hemodialysis for chronic renal failure died of staphylococcal pneumonia in the second week postoperatively after partial aortic arch replacement for chronic type A aortic dissection. The other death in group 2 occurred in a patient who underwent total aortic arch replacement with aortic valve replacement for recurrent aneurysm due to aortitis. Fatal multiple organ failure developed after hemorrhage from a graft implanted without preclotting.

Postoperative hemorrhage requiring rethoracotomy occurred in 1 patient each in groups 1 and 2. No serious postoperative cerebral complications were seen in any of the patients who survived the operation, and no paraplegia due to spinal cord ischemia was noted in either group. Respiratory failure that required the aid of a respirator for more than 5 days after the operation occurred in 1 patient in group 1 and 7 in group 2.

Renal failure, defined as a blood urea nitrogen level of more than 25 mmol/L (70 mg/dL) or a serum creatinine level of more than 265 μmol/L (3.0 mg/dL), occurred in 3 patients in group 1 and 4 in group 2. Hepatic failure, defined as a total bilirubin level of more than 51 μmol/L (3.0 mg/dL) or a glutamic-pyruvic transaminase level of more than 100 units, occurred in 2 patients in group 1 and 5 in group 2. No significant differences between the two groups were seen in the rate of postoperative complications, including hemorrhage, respiratory failure, renal failure, and hepatic failure.

The data concerning extracorporeal circulation in the

Table 3. Surgical Results

Variable	Group 1	Group 2	p Value
No. of patients	9	23	
Early death	1 (11.1%)	2 (8.7%)	NS
Postop complications			
Hemorrhage	1	1	NS
Cerebral complication	0	0	NS
Paraplegia	0	0	NS
Respiratory failure	1	7	NS
Renal failure	3	4	NS
Hepatic failure	2	5	NS
Late death	2	1	NS

NS = not significant.

Table 4. Extracorporeal Circulation Data

Variable	Group 1	Group 2	*p* Value
Total bypass time (min)	148 ± 31	233 ± 55	<0.01
Cooling time (min)	27 ± 9	36 ± 13	NS
Cardiac arrest time (min)	103 ± 27	173 ± 49	<0.01
Rewarming time (min)	36 ± 10	51 ± 17	<0.02
Lowest rectal temp (°C)	24.4 ± 3.1	21.8 ± 1.5	<0.01
Lowest core (head) temp (°C)	23.1 ± 3.9	21.2 ± 1.5	NS
SCP flow (mL/min)	616 ± 41	577 ± 83	NS
SCP pressure (mm Hg)	58 ± 12	42 ± 12	<0.02
SCP time (min)	68 ± 21	90 ± 27	NS
Systemic low-flow perfusion time (min)		72 ± 28	
Systemic low-flow perfusion volume (mL/min)		538 ± 78	

NS = not significant; SCP = selective cerebral perfusion.

surviving patients in the two groups are compared in Table 4. The total bypass time was 148 minutes in group 1 and 232 minutes in group 2, whereas the cardiac arrest time was 103 minutes in group 1 and 173 minutes in group 2. Both times were significantly longer in group 2 ($p < 0.01$). No difference between the two groups was seen in the cooling period by extracorporeal circulation, but the rewarming period was significantly longer in group 2 than in group 1 (51 versus 36 min; $p < 0.02$). The lowest rectal temperature was also significantly lower in group 2 than in group 1 (21.8° versus 24.4°C; $p < 0.01$). The cerebral perfusion time was 68 minutes in group 1 and 90 minutes in group 2, and no significant difference was noted between the two groups. The mean systemic low-flow perfusion time during open aortic anastomosis was 72 minutes in group 2.

Late death occurred in 2 patients in group 1 and 1 patient in group 2. The causes of death were renal failure or multiple organ failure, and all of these patients had renal impairment with a creatinine clearance of 30 mL/min or less preoperatively.

The other 26 surviving patients are currently leading normal lives and have been followed up for from 2 months to 4 years postoperatively.

Comment

Patients with aortic arch aneurysms have the highest operative morbidity and mortality among all those undergoing operation for aneurysms of the thoracic aorta. Since the establishment of cardioplegia as a method of protecting the myocardium, the appropriate selection of operative procedures that prevent cerebral ischemia during reconstruction of the aortic arch has become important in improving the operative results for these patients.

Selective cerebral perfusion has been used as a support procedure to prevent cerebral ischemia, but the optimum details of the perfusion technique, including the site of cerebral perfusion, the rate of perfusion, the temperature of the perfusate, and the perfusion pressure, have not yet been established and each institution currently uses its own methods. Therefore, the results obtained with this method are quite variable at present, and a major disadvantage is that SCP is rather more complicated than HCA.

For these reasons, the simple HCA procedure, which does not require special equipment or cannulation of the arch vessels, has recently been applied clinically to prevent cerebral ischemia during aortic arch reconstruction, and the operative results for aortic arch aneurysms have subsequently improved. We have previously compared the use of SCP and HCA in aortic arch aneurysm operations and found that both methods gave satisfactory results regarding the prevention of cerebral ischemia [17]. However, with HCA there is a limit on the duration of cerebral circulatory arrest, which is generally thought to be about 1 hour [19, 20]. In our previous experimental study, the safe time limits were 30 minutes when the rectal temperature was 20°C and 60 minutes when it was 15°C [21]. Therefore, we currently use SCP in cases where the cerebral circulatory arrest time exceeds 45 minutes. Griepp and associates [8] have applied deep hypothermia (about 15°C) and circulatory arrest in the treatment of aortic arch aneurysms with satisfactory results. However, this technique has a few problems such as coagulopathy and pulmonary insufficiency due to the deep hypothermia and the prolonged period of cardiopulmonary bypass needed for cooling and rewarming. Therefore, Livesay and co-workers [11] recommended the use of moderate hypothermia (20° to 24°C), but the problem with their technique was that the safe limit of cerebral circulatory arrest was only 30 minutes. Accordingly, because of limitations on the duration of cerebral circulatory arrest, it seems to be necessary to select SCP in patients for whom the aortic arch occlusion time is expected to exceed 60 minutes.

In our hands, about 60 minutes is required for total replacement of the aortic arch. In patients with aortic arch dissection it is probably safer to select SCP from the beginning, because it is often difficult to estimate preoperatively the time required for obliteration of the distal false lumen, performance of the distal graft anastomosis, and reconstruction of the aortic arch.

The arch vessels used for cerebral perfusion differ from institution to institution when SCP is used, but both the LCCA and right common carotid arteries are generally used. However, for cerebral perfusion on the right side the IA (as in our series) or the right axillary artery is also used. Bloodwell and colleagues [2] reported that the IA, LCCA, and LSA should be used for perfusion to prevent the subclavian steal phenomenon. However, a recent study showed that perfusion of the LSA was not necessary as long as the aortic arch was not occluded for a long period [5]. Frist and associates [6] reported that unilateral cerebral perfusion through the LCCA or IA was sufficient to prevent cerebral ischemia at a temperature of 26° to 28°C. However, when performing unilateral cerebral perfusion, it is necessary to confirm preoperatively that there is no severe carotid stenosis and that the circle of Willis is patent. Thus, this method has the disadvantage that such confirmation cannot always be obtained preoperatively in the case of an emergency operation.

In addition to the site of perfusion, the rate of perfusion is also important, because both hyperperfusion and hypoperfusion can cause cerebral damage. Under normothermic conditions, perfusion at about 900 mL/min is sufficient, but the optimum perfusion rate varies in accordance with the temperature of the perfused blood and the cerebrovascular resistance.

In our series, we used both the IA and LCCA as the site of perfusion at a rectal temperature of 22° to 25°C. Selective cerebral perfusion was performed at a rate of 10 $mL \cdot kg^{-1} \cdot min^{-1}$ using a single roller pump separately from the systemic circulation. Bilateral cerebral blood flow mainly depends on the cerebrovascular resistance on each side of the brain, and the cerebral perfusion pressure was adjusted by monitoring the right radial artery pressure, which was maintained at 50 to 70 mm Hg. This method is simpler than that in which perfusion is performed separately from the systemic circulation through the bilateral common carotid arteries using two pumps and the pressure of the bilateral superficial temporal arteries is monitored. It also has the advantage of providing perfusion for at least the right vertebral artery.

When using an open aortic anastomosis, it is possible to extend the graft replacement as far as the descending aorta just distal to the LSA through only a median sternotomy. Thus, this method has the advantage of preventing the increased risk of hemorrhage and complications such as lung damage associated with left thoracotomy. Moreover, it is possible to prevent crush injuries to a fragile aorta in acute aortic dissection by avoiding clamping, and it is easier to obliterate the false lumen and perform the distal graft anastomosis in a bloodless operative field [7, 15]. Therefore, we have used open aortic anastomosis concomitantly with SCP since 1987.

No significant difference was seen in hepatic and renal complications between group 1, which received perfusion of the lower half of the body from the femoral artery at a flow rate of 40 $mL \cdot kg^{-1} \cdot min^{-1}$ at a rectal temperature of 25°C, and group 2, which had perfusion of the lower half of body at a flow rate of 0.5 to 1.0 L/min at a rectal temperature of 22°C. The systemic low-flow perfusion time in group 2 was 72 minutes, but no paraplegia related to spinal cord ischemia developed postoperatively. Thus, ischemia of the abdominal viscera and the spinal cord was prevented in group 2.

Group 2 had a higher rate of associated diseases than group 1, and therefore, the procedures performed extended the time required for extracorporeal circulation. In addition, there were more emergency operations in group 2, so respiratory failure tended to appear more often as a postoperative complication.

To shorten the duration of cooling and rewarming by extracorporeal circulation, a method has been devised whereby the descending aorta is occluded with an intraluminal balloon and moderate systemic cooling to 26° to 28°C is used [6]. This method has the disadvantages that the balloon obstructs the operating field and that safe and reliable occlusion of the descending aorta is difficult to obtain in patients with acute aortic dissection.

The cerebral perfusion time in group 2 averaged 90 minutes, which was longer than the systemic low-flow perfusion time, and this was because there were many cases where the proximal graft anastomosis was performed under cerebral perfusion after reconstruction of the aortic arch.

Selective cerebral perfusion has the advantage of preventing cerebral ischemia for a longer period than HCA and of reducing stress on the surgeons because there are no strict time limits imposed on the reconstruction of the aortic arch. However, its disadvantage is that cannulation of the arch vessels is necessary, and these vessels might be damaged by extension of the dissection. In our series, extension of the dissection was usually limited to the origins of these arteries, and no difficulties arose after cannulation of arch vessels distal to the lesion.

In conclusion, despite being more complicated than HCA, SCP appears to be a useful procedure for preventing cerebral ischemia during complex reconstruction of the aortic arch in patients with thoracic aortic aneurysms, as it avoids the need for an operative time limit. By performing open aortic anastomosis concomitantly, it is possible to simplify the operative procedure and improve the results of this type of operation.

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Effect of Internal Mammary Artery Dissection on Sternal Vascularization

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Internal mammary artery (IMA) dissection may cause sternal devascularization and ischemia resulting in sternal wound complication. To evaluate the effect of median sternotomy and IMA dissection on sternal vascular supply, sternal bone tomography was performed 7 days and 1 month after cardiac operation in 67 patients. Seventeen nondiabetic patients had single IMA grafts, 18 had double IMA grafts, and 12 had only saphenous vein grafts or valve replacement. Twenty diabetic patients were studied after any one of these operations. Seven patients were restudied 1 month after the operation. Sternal technetium-99m–methylene diphosphate tomography was performed. The sternum was visualized and focal zones of hypoactivity represented sternal hypoperfusion. The ratio of hypoactivity area over total sternal area was calculated for every patient. After median sternotomy without single or double IMA grafts, the averaged hypoperfusion ratio was 4% ± 1% compared with 13% ± 3% after single IMA grafts and 24% ± 6% after double IMA grafts ($p < 0.0001$). Diabetic patients without IMA, with single IMA, and with double IMAs showed hypoperfusion areas of 5% ± 3%, 15% ± 5%, and 23% ± 9%, respectively, a result similar to that of nondiabetic patients. One month after operation the hypoperfusion area decreased to 2% ± 2% ($p < 0.05$) in restudied patients. Our results indicate that IMA dissection causes a significant although partial and temporary sternal ischemia, which is more severe after double IMA than single IMA mobilization and which may be incriminated in the development of sternal wound infection. This vascularization defect was not greater among patients with diabetes mellitus.

(Ann Thorac Surg 1992;53:115–9)

The internal mammary artery (IMA) graft has superior early and long-term patency rate as compared to saphenous vein grafts [1]. Patients with a left IMA graft to the anterior myocardial wall have improved long-term survival and decreased rate of reoperation and late cardiac events [2–4]. These excellent clinical results reported with the use of the IMA suggest that patient longevity associated with one IMA graft might be further improved if two IMA grafts were used in patients with multivessel coronary artery disease requiring revascularization. Therefore, the use of bilateral IMA grafting has become more widely accepted. However, a greater incidence of wound complications [5, 6], particularly in diabetic patients [1, 7], has been reported. Partial devascularization of the sternum causing sternal ischemia was suggested as a contributing factor to the increase in wound infection rate after double IMA grafts [8, 9]. The present study was undertaken to evaluate sternal devascularization and ischemia after sternotomy and mobilization of one or two IMAs.

For editorial comment, see page 7.

Material and Methods

Patient Population

Sixty-seven patients who underwent cardiac operations between November 1989 and March 1990 at the Montreal Heart Institute were studied prospectively. They were divided into four groups according to the surgical technique used and the presence or the absence of diabetes. Twelve nondiabetic patients (group 1) underwent valve replacement or coronary bypass with saphenous vein only, and they served as the control group. In 17 patients (group 2), the left IMA was dissected free and a single IMA graft was performed either alone or in combination with vein grafts. In 18 patients (group 3), the left and right IMAs were used either alone or with vein grafts. Twenty patients with diabetes mellitus requiring medication who underwent valve replacement or coronary bypass grafting with vein grafts only (n = 5), one IMA (n = 8), or two IMAs (n = 7) form group 4.

To assess the homogeneity of these groups, clinical risk factors for sternal wound complications were studied (Table 1). Obesity was evaluated by the body mass index (body weight in kilograms divided by the square of the height in meters). Obesity was considered present in patients with an index of 30 kg/m^2 or more [10]. Angiographic characteristics of coronary anatomy were evaluated (Table 2). Stenosis greater than 50% of the luminal

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Table 1. Clinical and Operative Variables Among the Four Groups of Patients[a]

	Group			
Variable	1	2	3	4
No. of patients	12	17	18	20
Age (y)	60 ± 4	58 ± 2	56 ± 2	60 ± 2
Sex (men/women)	12 (100%)	13/4 (76%)	17/1 (94%)	18/2 (90%)
Obesity	1 (8%)	0	5 (28%)	5 (20%)
Reoperation	1 (8%)	0	0	2 (10%)
Emergency procedure	1 (8%)	1 (6%)	0	1 (5%)
Reexploration	2 (16%)	1 (6%)	1 (6%)	1 (5%)
Aortic cross-clamping time (min)	69 ± 6	56 ± 5	69 ± 5	61 ± 4
Cardiopulmonary bypass time (min)	114 ± 10	95 ± 8	107 ± 8	103 ± 6

[a] Where applicable, data are shown as the mean ± the standard error of the mean.

diameter were considered hemodynamically significant. Ejection fraction was determined from left ventriculography in 54 patients.

Perioperative Protocol

All patients except those who underwent an emergency procedure were submitted to the same protocol before operation: search for possible infection (especially of dental, respiratory, and genitourinary origin) and preoperative treatment when needed, shaving of the operative site, and showering with an antiseptic soap. Prophylactic antibiotic (cefamandole) treatment was started at the induction of anesthesia and continued during 48 hours at doses of 1 g every 6 hours.

Radionuclide Imaging

The sternal area of devascularization and ischemia was evaluated by sternal bone scan tomography performed 7 days after cardiac operation [11]. In 7 patients, 5 from group 3 and 2 from group 4, the scan was repeated 1 month after operation.

All patients underwent single photon emission computed tomography of the sternum 3 hours after the intravenous injection of 25 mCi of technetium-99m–methylene diphosphate. Sixty-four projections of 20 seconds each were acquired over a 180-degree anterior arc (90 degree left lateral to 90 degree right lateral) with a variable elliptical orbit on a 64 × 64 × 16 byte matrix. Image processing was done using filtered back projection with a Butterworth filter (cutoff, 0.7; order, 8). No attenuation or scattered correction algorithm was used. Oblique slices, one pixel thick (6.4 mm), were reconstructed parallel to the long axis of the sternum. A global sternal image was created by summing four to six oblique slices containing sternal activity.

Table 2. Cardiac Catheterization Data

	Group			
Variable	1	2	3	4
No. of patients	9	17	18	20
Coronary disease				
One vessel	1 (11%)	1 (6%)	0	0
Two vessels	2 (22%)	5 (29%)	5 (28%)	0
Three vessels	6 (67%)	11 (65%)	13 (72%)	16 (100%)
Left ventricular ejection fraction	0.55 ± 0.3	0.51 ± 0.5	0.58 ± 0.3	0.51 ± 0.5

Regions of interest were drawn over sternum and on sternal areas with no or minimal uptake by an experienced nuclear medicine physician blinded to the clinical data. For each patient, the ratio of the number of pixels in hypoactive areas over the total sternal area was assessed. Hypoactive areas were classified as involving the manubrium or the upper, middle, or distal third of the sternum and as being left-sided, right-sided, or bilateral.

Statistical Analysis

The statistical analysis was performed using univariate analysis, analysis of variance, and Fischer's exact test when appropriate. Statistical significance was established at 95%. Data are expressed as mean ± standard error of the mean.

Results

The four groups of patients were similar with respect to age, sex, incidence of obesity, reoperation and emergency procedures, reexploration for bleeding, and averaged clamping and cardiopulmonary bypass times (see Table 1). Extent of coronary artery disease and left ventricular function were also similar among the four groups (see Table 2).

No significant alteration in sternal blood flow was shown after sternotomy without IMA dissection (group 1). The ratio of sternal hypoperfusion area was 4% ± 2% (mean ± standard error of the mean). After mobilization of one (group 2) or two IMAs (group 3), sternal vascular-

Table 3. Ratio of Hypoperfused to Total Sternal Area

	Nondiabetic Patients		Diabetic Patients (group 4)	
Group	No. of Patients	Ratio[a] (%)	No. of Patients	Ratio[b] (%)
No IMA	12	4 ± 1	5	5 ± 3
Single IMA	17	13 ± 3	8	15 ± 5
Double IMA	18	24 ± 6	7	23 ± 9

[a] $p < 0.05$ between groups. [b] p = not significant.

ization was significantly impaired compared with the first group of patients, with respective hypoperfusion ratio areas of 13% ± 3% and 24% ± 6%, a significant difference ($p < 0.05$) (Table 3). In those patients, the left side of the sternum was involved at all times with no preponderance in terms of the level implicated (proximal versus distal). Bilateral involvement was significantly more common after double IMA grafting (20/25, 80%) than after single IMA grafting (2/25, 8%, $p < 0.00001$) and constantly implicated the distal sternum.

Among the group of diabetic patients (group 4), similar ratios were observed when compared with respective groups 1, 2, and 3, according to the surgical technique used, and no significant differences were found (see Table 3). One month after operation, the ratio of sternal devascularization decreased from 22% ± 8% to 2% ± 2% ($p < 0.05$) in the studied patients (Fig 1).

There was no death in the patients of this study. Wound complications developed in 4 male patients (6%): 3 among the 25 patients with double IMA grafts (12%), 1 in the 25 patients with single IMA grafts (4%), and none among the 17 patients without IMA grafts, a nonsignificant difference. A mediastinitis due to *Staphylococcus aureus* developed in 1 diabetic patient with bilateral IMA grafts. His area of sternal devascularization was 38% one week after the operation. He was readmitted 15 days after the initial operation and treated with intravenous antibiotics, sternal debridement, and continuous irrigation with iodine. An omental flap reconstruction was successfully performed 16 days after debridement. Two other patients with bilateral IMA grafting required rehospitalization and reoperation, 1 for superficial wound infection with *Staphylococcus epidermidis* (no area of sternal hypoperfusion) and the other for aseptic sternal dehiscence resulting from wire suture cutting through the sternum. The last patient had a ratio of sternal hypoperfusion of 38%. Superficial wound dehiscence and infection caused by *Staphylococcus epidermidis* after IMA dissection (an emergency operation) was managed by frequent dressing changes and systemic antibiotics (no area of sternal hypoperfusion). Complete healing without sequelae was obtained in all 4 patients.

Comment

It has been shown that late survival and freedom from cardiac events are improved when at least one IMA graft is used compared with saphenous vein graft alone [2, 4]. Grondin and associates [12, 13] reported that nearly 50% of saphenous vein coronary grafts are occluded by the tenth postoperative year. In contrast, 95% of IMA grafts remained patent, and no evidence of clinical deterioration occurred up to 10 years postoperatively [14]. The occurrence of serious atherosclerosis in grafted IMA appears to be rare [4, 15]. Injury during preparation of the IMA and technical errors are the only significant causes of IMA failure after operation [3]. Moreover sequential angiographic studies have shown that IMA grafts may enlarge with time, suggesting that this arterial conduit is capable of adaptation to provide the blood flow required to meet myocardial needs [16].

Recent data [7, 14] suggest a survival benefit for patients with double IMA grafts versus one IMA among hospital survivors. Patients with two IMA grafts had significantly improved freedom from subsequent myocardial infarction, recurrence of angina pectoris, and subse-

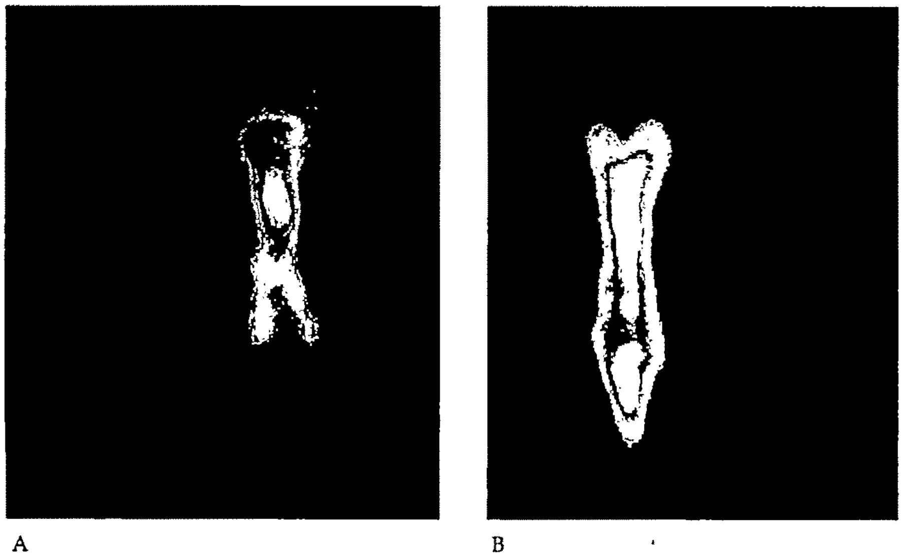

Fig. 1. (A) Sternal scintitomogram obtained 1 week after a bilateral internal mammary dissection. Bone uptake is increased at the manubriosternal junction. There is no or minimal uptake of the radioactive tracer by the distal third of the sternum. The area of hypoperfusion involves 35% of the total sternal area. (B) Follow-up study performed on the same patient 1 month after operation. There is diffuse and homogeneous increased uptake in the sternum adjacent to the sternotomy. No area of hypoactivity is seen.

quent total ischemic event. Improved freedom from coronary interventional therapy (percutaneous transluminal coronary angioplasty and reoperation) is also found when two IMA grafts have been used. These results are in contrast with the increase in the attrition rate of saphenous vein grafts observed after 10 years. However, bilateral IMA grafting has been reported to increase the incidence of wound complications. Several mechanisms may be involved, including additional operative time for the surgical procedure, difficult and limited exposure for IMA dissection [17], and increased bleeding and reexploration rates.

Two studies [8, 9] have reported that mobilization of one IMA leads to significant devascularization of the ipsilateral hemisternum whereas complete sternal devascularization occurs with bilateral IMA dissection. In an anatomical study [8], Arnold demonstrated that the sternal circulation is derived solely from a periostal plexus that arises from segmental sternal branches of the IMAs. When one IMA is dissected, revascularization of that side of the sternum may occur by crossover collaterals from the unharvested side with intact blood supply. Of course, it depends on a good and stable contact between the two sternal sides. According to the same study, bilateral IMA mobilization would result in complete sternal devascularization. However, he failed to inject the intercostal arteries, another source of collateral flow [17].

Seyfer and associates [9] showed no evidence for collateral flow to the sternum that could immediately substitute for the missing IMA, with a 90% decrease in sternal blood flow after mobilization of one IMA. Therefore, these studies suggest that the sternum must heal like a free bone graft after bilateral IMA harvesting. This could explain the higher rate of sternal wound complication and particularly infection after bilateral IMA dissection. Moreover, decreased sternal blood flow jeopardizes local immune response and optimal antibiotic level when contamination occurs.

In the present study, the highest ratio of devascularization was 46% of the total sternal area, indicating that bilateral IMA mobilization causes an important but only partial decrease in sternal blood supply. However, tomographic examinations were performed 7 days after the operation because of the technical difficulty in performing this examination. Perhaps an earlier study would have shown an even more extensive devascularization of the sternal bone.

Nevertheless, double IMA grafts cause a significant ischemia of the sternal bone as compared with single IMA or simple median sternotomy without IMA harvesting. In addition, diabetes mellitus did not increase the sternal area of devascularization, suggesting that the increased risk of wound infection in this group of patients is not solely related to sternal ischemia.

Another finding of this study was that the decrease in blood supply to the sternal bone is transient and is almost completely reverted 1 month after operation. This partial and transient sternal ischemia seems to indicate that collaterals, although poorly developed, are usually sufficient for sternal healing. This collateral circulation occurs at least in part from intramedullary and periostal blood flow supplied by the contralateral side when only one IMA has been harvested, or from intercostal arteries.

Although wound complications are not uncommon, sternal infection with mediastinal involvement is a rare complication after open heart operations, with a reported incidence of 0.4% to 5% [6, 18–21]. The latter is a serious and life-threatening complication [19, 20] with a prolonged morbidity among surviving patients. Moreover, this complication has substantial economic implications [21]. Consequently, the increased risk of sternal wound complication after bilateral IMA grafting should be a strong incentive for strict aseptic measures during operation, restricted personnel circulation in the operating room, cautious use of the electrocautery for preparing the IMA graft, and minimal use of intramedullary bone wax [22]. In addition, bilateral IMA grafts should probably be avoided in patients at risk for sternal wound complication such as diabetic patients, elderly patients, and patients with chronic obstructive pulmonary disease [1, 5, 7, 22, 23].

In conclusion, better early and long-term results with bilateral IMA grafting are a strong incentive for its use in selected patients, despite the slight increase in the risk of sternal wound complications. The transient and partial sternal devascularization observed after IMA dissection, particularly in double IMA grafts, appears to be a significant factor in the development of sternal wound complications.

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Repeat Mediastinoscopy in the Assessment of New and Recurrent Lung Neoplasm

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From 1976 to 1990, 140 patients (mean age, 66 years; 91% male) underwent repeat mediastinoscopy as a routine staging procedure. The mean interval between first and second mediastinoscopy was 56 months. Owing to adhesions, 26 repeat mediastinoscopies (18%) were considered incomplete. There was no mortality, and 10 complications did not require interventional therapy. The results were positive in 20 patients, thus avoiding an unnecessary thoracotomy. In 7 patients with negative findings, positive lymph nodes were found at thoracotomy or by transcarinal puncture biopsy. The sensitivity of repeat mediastinoscopy in this series is 74%, and the accuracy 94%. We consider repeat mediastinoscopy a safe and reliable preoperative staging procedure in new or recurrent lung cancer.

(Ann Thorac Surg 1992;53:120–2)

In 1974, Palva [1] stated that mediastinoscopy is a procedure that, as a rule, should not be repeated. In his series only 1 of the 330 patients underwent repeat mediastinoscopy. Severe fibrosis between the innominate artery and the trachea presented substantial technical difficulty. On the basis of this experience, some writers [2] have gone even further and considered repeat mediastinoscopy as contraindicated. The development of pretracheal fibrosis was confirmed on a histological basis by Balle and Bretlau [3]. Authors of later series [4, 5] considered a previous mediastinoscopy only as a relative contraindication, and stated that repeat mediastinoscopy should be done whenever it could contribute to the diagnosis.

We support the opinion that routine mediastinoscopy provides essential information for the staging and management of lung cancer [6]. A previous mediastinoscopy is not considered a contraindication and does not change this policy. In this study we reviewed our experience with 140 repeat mediastinoscopies.

Material and Methods

Between 1976 and 1990, repeat mediastinoscopy was performed in 140 patients, 127 men (91%) and 13 women (9%) ranging from 43 to 82 years old. Results were reviewed retrospectively. In all but 1 patient the first mediastinoscopy revealed only benign lymphatic tissue. Twelve patients underwent the first mediastinoscopy for nonmalignant disease. The mean interval between first and second mediastinoscopy was 56 months, ranging from 3 months to 16 years. All accessible lymph nodes were sampled and mapped according to the American Thoracic Society's "Clinical Staging of Primary Cancer of the Lung" [7, 8]. A mediastinoscopy was considered complete if on both sides the tracheobronchial nodes (Naruke 4) and the main carinal node (Naruke 7) were reached.

Results

Twenty (14%) of the 140 remediastinoscopies performed showed positive mediastinal lymph nodes. In 2 of these patients a resection was nevertheless performed: 1 patient with a positive lymph node at the tracheobronchial corner had a right pneumonectomy, and 1 patient with a subcarinal lymph node had a left pneumonectomy with carina resection. In both patients the positive result of the mediastinoscopy was confirmed at thoracotomy. In the other 18 patients no thoracotomy was performed. One hundred twenty repeat mediastinoscopies were negative. In 20 patients this was not followed by further operation: in 11 because no evidence of malignancy was found, in 3 because another treatment (chemotherapy or radiotherapy) was chosen, and in 6 because irresectability was confirmed by other techniques. In 2 of these 6 patients the repeat mediastinoscopy was considered incomplete by the surgeon and a transcarinal puncture biopsy was positive. One patient had invasion of the esophagus, 1 patient a metastatic pleural effusion, and 2 patients distant metastases that became clear only after the mediastinoscopy. In 3 of the remaining 100 patients an anterior mediastinotomy showed invasion of the aortopulmonary space, intrapericardial invasion, and invasion of the dorsal mediastinum. Therefore, 97 patients with a negative mediastinoscopy underwent thoracotomy. Six tumors proved to be irresectable at thoracotomy (negative mediastinal lymph nodes, 2; positive mediastinal lymph nodes, 2; no lymph node dissection, 2). Ninety-one patients underwent a resection: 33 pneumectomies, 34 (bi-)

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Table 1. Cross-Tabulation of the Histology of the First and Second Tumor

	Second Histology							
Initial Histology	Squamous Cell	Adenocarcinoma	Mixed Cell	Small Cell	Large Cell	Benign	Unknown	Total
Squamous cell	71	5	3	2	1	8	2	92
Adenocarcinoma	1	10	1			2		14
Mixed cell	3		1					4
Small cell anaplastic	2			3				5
Large cell anaplastic	3	2			1	2		8
Benign	7	1		1	1	2		12
Unknown	3					1		4
Hodgkin						1		1
Total	90	18	5	6	3	16	2	140

lobectomies, 14 segmentectomies, 9 wedge resections, and 1 sleeve resection of the left main bronchus. Of the 91 patients who underwent resection, 5 were found to have benign lesions.

For the calculation of sensitivity and accuracy we did not take into account the 16 patients in whom no malignancy could be shown (11 without further operation and 5 with operation for a benign lesion). We also did not consider the 4 patients who were not operated on because of the presence of invasion or metastases, the 3 patients in whom no thoracotomy was performed despite a negative mediastinoscopy, the 3 patients with positive anterior mediastinotomy, and 2 patients who underwent thoracotomy but in whom the lesion proved to be irresectable and no additional lymph node dissection was performed. We did include the 2 patients with a positive transcarinal puncture as false-negative results. This gives us a total of 112 patients, of whom 20 had a positive mediastinoscopy and 90 underwent thoracotomy after a negative mediastinoscopy. During this thoracotomy an extensive staging of all accessible lymph nodes was always performed. Eleven of these patients had positive N2 nodes, of which 5 should normally have been in the reach of the mediastinoscopist. In 3 of these patients the mediastinoscopy was considered incomplete by the surgeon. This implies that of a total of 92 negative remediastinoscopies, 7 have to be considered as false negative. Repeat mediastinoscopy can, therefore, in our hands be performed with a sensitivity of 74%, specificity of 100%, and accuracy of 93%.

During these 140 repeat mediastinoscopies a total of 381 lymph node stations were biopsied (mean, 2.7). Twenty-six explorations (18%) were considered by the surgeon as incomplete: 24 due to adhesions and 2 due to bleeding. In 82% a complete or sufficient exploration of the pretracheal and paratracheal spaces was possible. The mean time between first and second mediastinoscopy for the procedures that were considered incomplete was 42 months, which is less than the 56 months for the group as a whole.

There were no deaths due to the procedure. There were no complications necessitating surgical intervention. In 6 patients bleeding occurred, which always stopped by simple tamponade. In 2 patients this bleeding caused premature ending of the procedure. Two esophageal biopsies healed without further treatment. Recurrent nerve palsy occurred once, and there was one wound infection. This means a total of 10 complications (7%), of which none can be considered serious or life-threatening.

The histology of the primary and secondary tumors are cross-tabulated in Table 1. Squamous cell carcinoma is the most frequent tumor in both groups. Fifty percent of all patients had a squamous cell carcinoma as both the first and the second tumor. American Joint Committee on Cancer staging of the 92 malignant tumors with negative mediastinoscopy that underwent thoracotomy showed that 2 patients were in stage 0, 55 in stage I, 10 in stage II, 21 in stage IIIa, and 4 in stage IIIb.

Comment

In earlier discussions about repeat mediastinoscopy, the number of cases was rather limited, making analyses of the data perilous (Palva and associates [9], 6 patients; Lewis and co-workers [4], 12 patients; Balle and Bretlau, 4 patients).

It has been reported that mediastinoscopy should never be repeated, because of problems encountered while dissecting the adhesions between the innominate artery and the trachea. In our series the mediastinum could always be reached by direct dissection of the adhesions or by following the left lateral wall of the trachea, thus avoiding the critical innominate artery–tracheal area. In many operative reports, scar tissue was reported to make the exploration more laborious, preventing the complete inspection of the mediastinum in 18% of the procedures. This did result in a loss of sensitivity in our series (74%) compared with an expected sensitivity of about 85% in primary mediastinoscopy. A useless exploration by thoracotomy was avoided in 18 patients (15%), and the procedure contributed to a successful resection in 86 patients. The procedure reached an accuracy of 93%.

Scarring can blur the difference between lymph nodes and other vital structures. Careful dissection resulted in an acceptable complication rate with no major complications and a 7% rate of minor complications. All procedures were performed by a small team of surgeons, increasing the experience and reducing the risks.

Once the mediastinum has been opened, tissue planes and interfaces can be changed, as pointed out by Lewis and associates [4]. Therefore computed tomographic scan, unable to distinguish hyperplastic, anthracotic, or granulomatous nodes from malignant nodes, becomes even less reliable after previous mediastinoscopy. For this reason we think repeat mediastinoscopy is even more important as a preoperative staging procedure in patients who have undergone previous mediastinoscopy. It should be performed in every patient with suspicion of a new or recurrent lung carcinoma before thoracotomy is planned.

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INVITED COMMENTARY

Because, in my opinion and that of my colleagues, mediastinoscopy has always been considered the most important, definitive staging procedure for carcinoma of the lung, almost all of our patients have this procedure before an anticipated resection. In our experience, the computed tomographic scan does not consistently and accurately reveal the mediastinal contents, so we still rely on mediastinoscopy. In fact, it is not unusual for the computed tomographic scan to present either false-negative or false-positive findings for lymph nodes in the mediastinum. It cannot differentiate benign anthracotic, hyperplastic, or granulomatous nodes from truly malignant nodes. After a mediastinoscopy has been performed, which results in disruption of tissue planes and scar formation, future computed tomographic scans become even less reliable for the identification of mediastinal nodes. For these reasons and because mediastinoscopy allows bilateral visualization and palpation with direct biopsy, we remain strong advocates of mediastinoscopy.

In the past, repeat mediastinoscopy was considered to be contraindicated, because it was purported by prominent thoracic surgeons that it would be too hazardous to try to dissect the scarred mediastinum. In our experience, once the healed scar was excised and the strap muscles separated, the remainder of the procedure was not very difficult. On occasion, a patient will have a frozen mediastinum barring entry to this area. In the vast majority of repeat mediastinoscopies, however, the mediastinum can be satisfactorily entered and adequately explored, and the lymph nodes can be recovered. We have performed repeat mediastinoscopy since the early 1970s and are in complete agreement with the recommendations of Meersschaut and associates. Dr Meersschaut and colleagues are to be congratulated for their large and excellent series demonstrating the importance and feasibility of this most important staging procedure. Their findings and results continue to emphasize the need for repeat mediastinoscopy to remain a part of the armamentarium of the thoracic surgeon.

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Variation in Cryolesion Penetration Due to Probe Size and Tissue Thermal Conductivity

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The purpose of this study is to present data comparing the penetration of cryolesions created by various sizes and shapes of cryoprobes in human cadaveric myocardium, fat, and tissue of the central fibrous body. Ten cryolesions were made for each combination of tissue and cryoprobe studied. All cryolesions enlarged most rapidly during the first minute of cryothermia ($p < 0.01$). Maximal cryothermic penetration into nontrabeculated myocardium was 8.5 ± 0.5 mm (15-mm flat probe) and 6.1 ± 1.0 mm (5-mm small probe). Maximal cryothermic penetration into trabeculated myocardium was 9.4 ± 1.0 mm (10-mm cone-tipped probe) and 7.4 ± 0.5 mm (10-mm flat probe). Maximal cryothermic penetration into fat was 4.7 ± 0.7 mm (15-mm flat probe) and 3.9 ± 0.7 mm (5-mm flat probe). The deeper penetration of cryothermia into myocardium as compared with fat ($p < 0.05$) is related to the lower thermal conductivity of fat. Maximal cryothermic penetration of the central fibrous body was similar to that of the myocardium with transmural freezing of the central fibrous body after 4.4 ± 0.3 minutes of cryothermia. These data can be used when determining the optimal cryothermic exposure for ablation of arrhythmogenic tissue.

(Ann Thorac Surg 1992;53:123–6)

Cryothermia has been used successfully for the ablation of arrhythmogenic myocardium since 1977 when Mikat and colleagues [1] described the technique. Subsequent studies [2, 3] of cardiac cryosurgery demonstrated that the enlargement of cryolesions within ventricular myocardium varies substantially according to probe temperature, myocardial temperature, and myocardial perfusion. Similar studies to determine the penetration of cryolesions in different cardiac tissues that may be encountered during arrhythmia-ablating operations have not yet been published. The purpose of this study was to generate information describing the penetration of cryolesions made with various cryoprobe sizes in various cardiac tissues. This information is useful because surgeons generally rely on visual inspection, palpation, and knowledge of cryolesion enlargement in experimental preparations to determine the cryothermic exposure for any given clinical situation even though other methods for monitoring the enlargement of cryolesions have been described [3–5].

Material and Methods

Cryolesions were created in formalin-fixed excised cadaveric human hearts at room temperature (20° to 22°C). Cryolesions were made using expanding nitrous oxide cryoprobes with a flat surface (5 mm, 10 mm, or 15 mm in diameter) or a conical surface (base of cone, 10 mm in diameter).

To generate the cryolesions for comparison of the 5-mm and 15-mm flat-tip probes, one half of the probe was placed over a cut edge of nontrabeculated ventricular muscle or fat in the atrioventricular groove. Maximal freezing (ie, maximal pressure input against atmospheric pressure output) was initiated at time zero with the probe lightly touching the tissue. This produced probe temperatures from −60° to −65°C. Driveline pressure was maintained between 720 and 780 psi. Calipers were used to measure the depth of the cryolesion (Fig 1) at 1-minute intervals for 6 minutes. Only the 5-mm flat probe was used to freeze the central fibrous body. The time of transmural freezing of the central fibrous body was noted. Comparisons between the 10-mm flat probe and the 10-mm cone-tipped probe were conducted in trabeculated ventricular myocardium, again by placing half of the probe against the cut myocardial edge and measuring cryolesion depth every minute for 6 minutes. The flat probe sat on the top of the trabeculations, whereas the conical probe was gently wedged into the trabecular surface.

Ten cryolesions were made for each combination of tissue type and probe size. No tissue sample was frozen twice. The cardiac tissues were kept moist by immersing the heart in a buffered formalin solution between freezing trials.

Statistical analysis was performed using SAS-PC statistical software (SAS, Inc, Cary, NC). Within-group comparisons were made using Student's paired t test, and between-group comparisons were made with an analysis of variance procedure (General Linear Models procedure of SAS).

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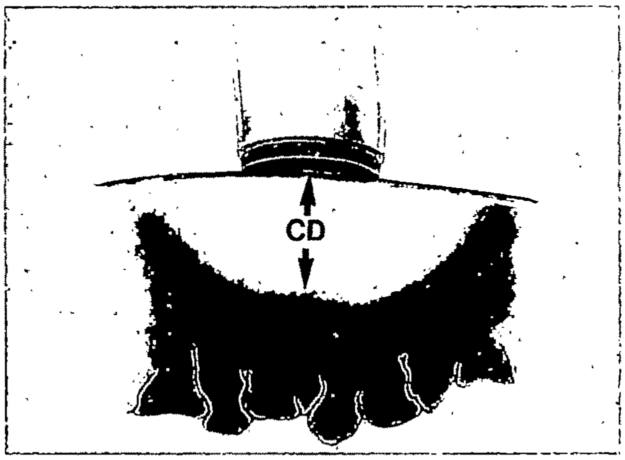

Fig 1. One half of each size of cryoprobe was placed over the tissue to be frozen. The depth of penetration into various tissues was measured at 1-minute intervals for 6 minutes. Cryolesion size was determined by measuring the grossly visible ice ball with calipers. (CD = cryolesion depth in millimeters.)

Results

In all tissues and with all probes, the most rapid expansion of the cryolesion occurred during the first minute of freezing ($p < 0.01$). The penetration rate of the ice ball then slowed to reach a maximal value (ie, asymptote of the penetration curve). The times to reach the asymptote of penetration for the various experimental combinations are listed in Table 1. These times ranged from 3.6 ± 0.3 minutes for the small probe in fat to 5.4 ± 0.3 minutes for the 10-mm cone-tipped probe in trabeculated ventricular myocardium. Graphic representations of cryolesion depth as a function of time are contained in Figures 2 through 4.

Figure 2 describes growth of the cryolesions generated by the small (5-mm flat) probe. The small-probe cryolesions penetrated further ($p < 0.001$) into the muscle as compared with fat. In Figure 3, the same finding ($p < 0.001$, fat versus muscle) is noted for the large (15-mm flat) probe. A between-group comparison of cryolesion penetration (ie, large-probe versus small-probe cryolesions in muscle; large-probe versus small-probe cryolesions in fat) shows significantly ($p < 0.01$) greater penetration for cryolesions made with the large probe in muscle. The difference between the penetration of cryolesions created with a large or a small probe in fat was not significant until the sixth minute of freezing ($p = 0.04$ at 6 minutes of freezing).

Table 1. Time to Asymptote of Cryolesion Penetration

Probe Type	Tissue Type	Time[a] (min)
5-mm flat	Fat	3.6 ± 0.3
5-mm flat	Muscle	4.9 ± 0.3
15-mm flat	Fat	4.6 ± 0.3
15-mm flat	Muscle	5.2 ± 0.3
10-mm flat	TM	4.7 ± 0.3
10-mm cone	TM	5.4 ± 0.3
5-mm flat	CFB	4.4 ± 0.3

[a] Data are shown as the mean ± the standard error of the mean.

CFB = central fibrous body (asymptote represents transmural freeze for CFB); TM = trabeculated myocardium.

Figure 4 compares the depths of cryolesions created with a 10-mm flat or cone-tipped probe in trabeculated myocardium. Pockets of air between frozen trabeculations were noted after the freezing of the ventricular surface with the flat probe. There were no air pockets between trabeculae frozen with a cone-tipped probe. The depth of the cryolesions created with a cone-tipped probe was significantly greater ($p < 0.001$) than the depth of cryolesions created with the flat probe.

In Figure 2, the penetration of cryolesions created with the 5-mm flat probe in the central fibrous body is described. Cryolesion penetration in the central fibrous body is similar to the penetration in ventricular myocardium and is significantly greater ($p < 0.01$) than cryolesion penetration into fat. The asymptote of cryolesion penetration in the central fibrous body represents the time required for transmural freezing. This occurred after 4.4 ± 0.3 minutes of cryothermia.

Comments

Cryothermia is currently used in the surgical treatment of a variety of atrial and ventricular arrhythmias [6, 7]. Real-time methods to determine the boundaries of a cryolesion have been described [3–5] but have not found wide clinical use. Instead, the enlargement of the cryolesion is usually monitored by visual inspection or palpation of the ice ball created during a cryothermic exposure. This information is combined with the surgeon's judgment based on previous experience as well as data describing the enlargement of cryolesions created under similar conditions in experimental animals. Previous studies [2, 3] have described the effects on cryolesion size of probe temperature, myocardial temperature, and the

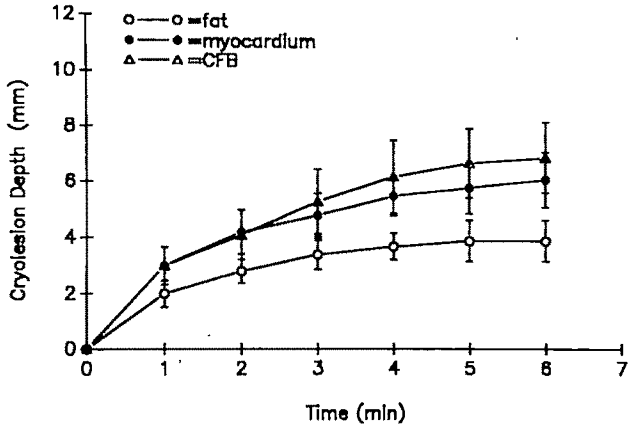

Fig 2. The expansion of cryolesions generated by a 5-mm flat cryoprobe in cardiac fat, myocardium, and tissue of the central fibrous body (CFB) was measured during 6 minutes of cryothermia.

presence or absence of myocardial perfusion (ie, normal perfusion or cardioplegic arrest with aortic cross-clamping). However, similar information describing cryothermic penetration with different probe sizes in a variety of cardiac tissues is not currently available.

Use of the optimal cryothermic exposure in any given situation is important for ablating the arrhythmogenic tissue while sparing the tissue outside the arrhythmogenic region from needless cryothermic injury. The tissue that is spared may include working myocardium, the specialized conduction system, valve tissue, or coronary arteries. It should be recognized that the measurements of cryothermic penetration obtained in this study were not intended for direct transfer to clinical cryosurgery. Rather, the present study was designed to provide information describing the relative enlargement rate (ie, penetration) of cryolesions created by different sizes and shapes of cryoprobes in a variety of cardiac tissues.

Engineers studying heat transfer in biological systems during the application of cryothermia have generated equations that quantitatively describe the temperature field produced around a cryoprobe as well as the rate of cryolesion enlargement under various conditions [8–11]. Three variables used in these equations are the initial temperature of the tissue, the initial temperature of the probe, and the heat generation resulting from blood flow. The importance of these three variables in determining the size of a cryolesion has been confirmed by previous studies [2, 3]. Two other variables included in these equations to predict cryolesion growth are cryoprobe radius and tissue thermal conductivity. Before this study, the effect of these two variables on the rate of cryothermic penetration in cardiac tissues had not been tested.

Cryoprobe radius can be changed by using a larger or smaller probe or by increasing the effective contact area of the probe-tissue interface. In the present study, the effect of variation in probe size on cryothermic tissue penetration was investigated by measuring cryolesion growth around a 5-mm or 15-mm flat cryoprobe held against the smooth epicardial surface of ventricular myocardium or fat. The study also compared cryolesion enlargement around a flat or cone-tipped 10-mm cryoprobe held against trabeculated ventricular myocardium. It was shown, as expected from the equations of Cooper and Trezek [8–10], that a larger probe-contact area produces a more deeply penetrating cryolesion.

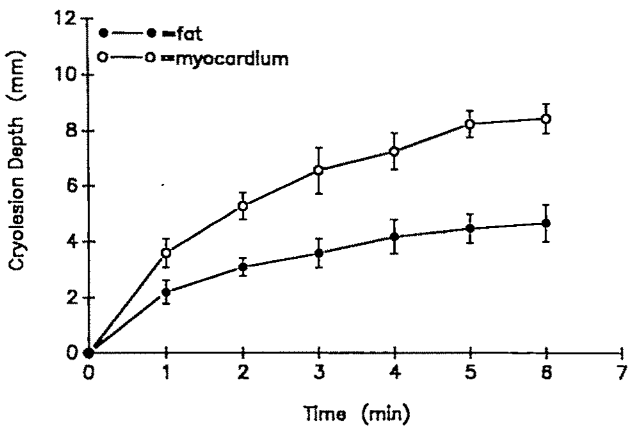

Fig 3. The cryolesions developing from a 15-mm flat probe placed on cardiac fat or myocardium were measured during 6 minutes of cryothermia.

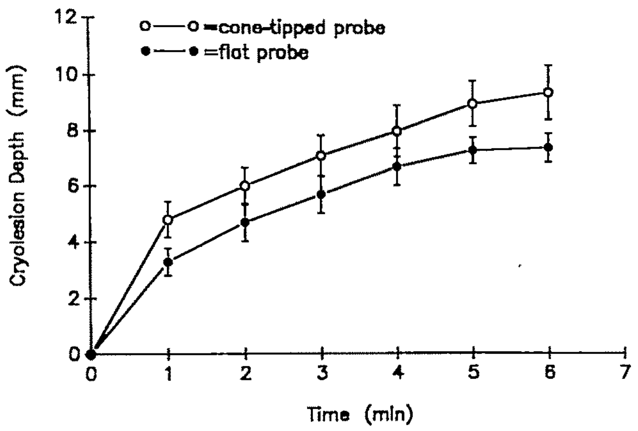

Fig 4. The depth of cryolesions produced by a flat or a cone-tipped cryoprobe in trabeculated myocardium was measured during 6 minutes of cryothermia.

The other question asked in this study is whether a discernible difference exists in the penetration of cryolesions produced in myocardium, fat, or tissue of the central fibrous body. It has been determined that the thermal conductivity of different human tissues is correlated with tissue water content [12] and that the thermal conduction constant for fat is considerably less than the constant for muscle [13, 14]. There are no data describing the thermal conduction constant for connective tissue similar to those for the central fibrous body. As predicted by the information regarding tissue thermal conduction constants, cryolesion growth was slower in fat than in myocardium. Cryolesion penetration of the central fibrous body was found to be similar to cryolesion penetration of myocardium.

The information provided by this study is intended to improve the surgeon's judgment in determining the optimal cryothermic exposure under a variety of circumstances. For example, the insulating effect of fat as compared with muscle must be remembered during cryoablation of accessory atrioventricular connections. The insulating effect of fat may protect major coronary arteries within the artioventricular groove from cryothermic injury [1, 15]; however, the insulating effect of fat may also protect an accessory pathway from a lethal cryothermic injury. Cryothermic obtundation with subsequent return of conduction may account for some of the recurrences seen using this method [16]. These data emphasize the importance of completely dissecting fat in the atrioventricular sulcus away from the muscle to be cryoablated to minimize recurrence of accessory pathway conduction after cryosurgery.

This study also describes the differential growth rate of cryolesions over time. The most rapid growth occurs during the first minute of cryothermic exposure, and the asymptote for growth is attained within 3 to 5 minutes after initiation of the freeze. This information is useful for planning an operation that includes the use of cryosurgery. For instance, expeditious cryoablation of a large region (eg, a large portion of the left ventricular endocardium) is best achieved using a probe with a large contact surface and multiple short (1- to 2-minute) cryothermic exposures. Relatively little is gained by extending the total time beyond 3 minutes.

The information regarding probe size and shape reinforces what is intuitively obvious. For a given cryothermic exposure time and temperature, a larger probe will penetrate more deeply into the myocardium than a smaller probe will. Improved contact between trabeculated muscle and the cone-tipped cryoprobe compared with the flat probe accounts for the superior cryoablating characteristics of the cone-tipped probe.

The information regarding freezing of the central fibrous body is useful for avoiding injury to the specialized conduction system. The central fibrous body freezes as rapidly as muscle and can be transmurally frozen. Therefore, caution must be used when cryoablating tissue in the vicinity of the central fibrous body, particularly during hypothermic cardioplegic arrest. The connective tissue of the central fibrous body has no special insulating properties, and permanent complete heart block will occur if the His bundle is frozen.

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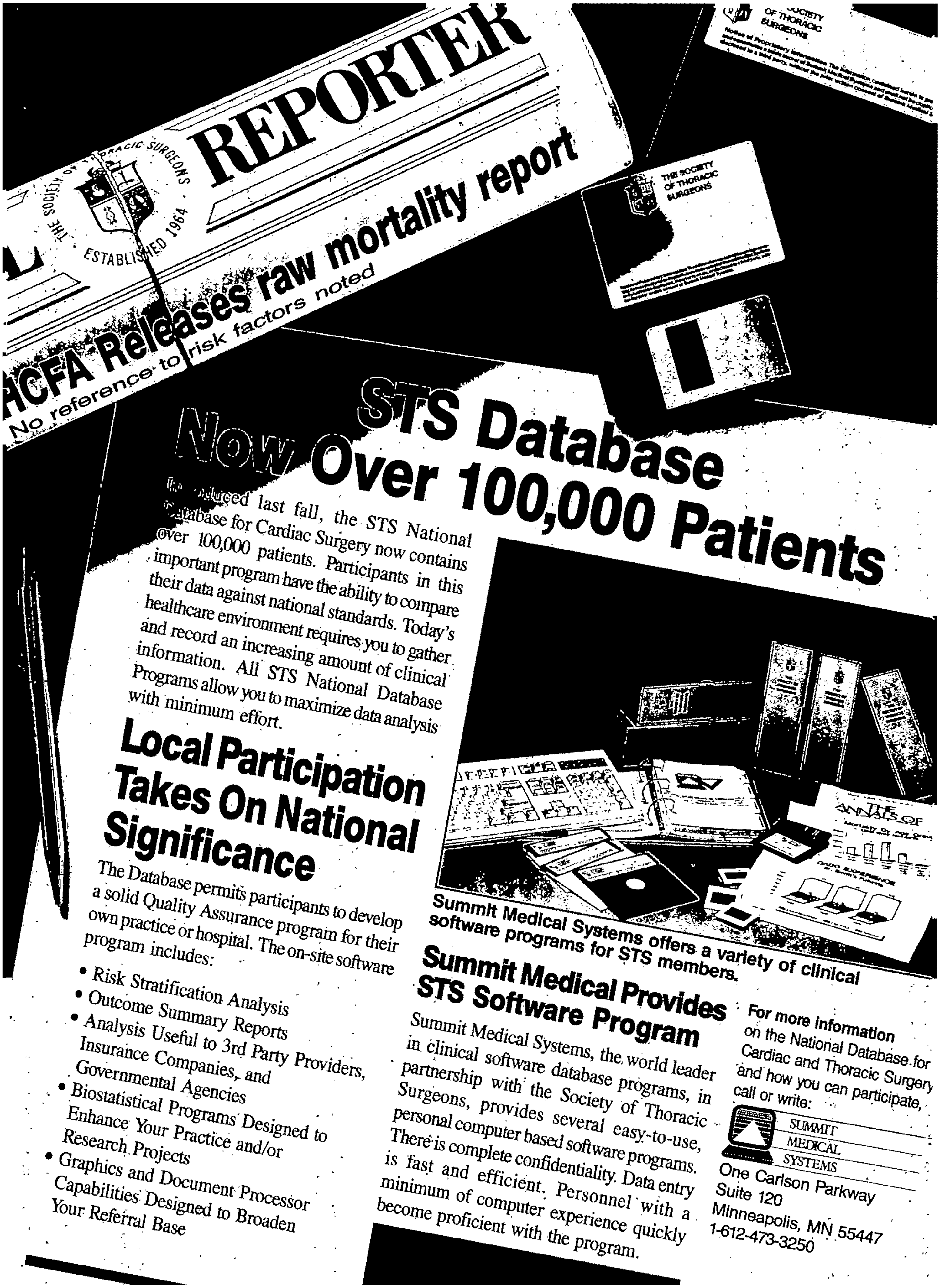

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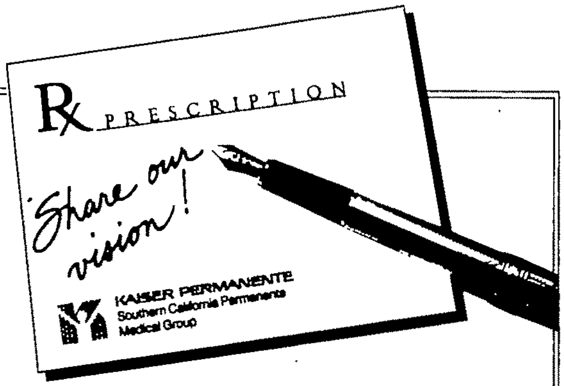

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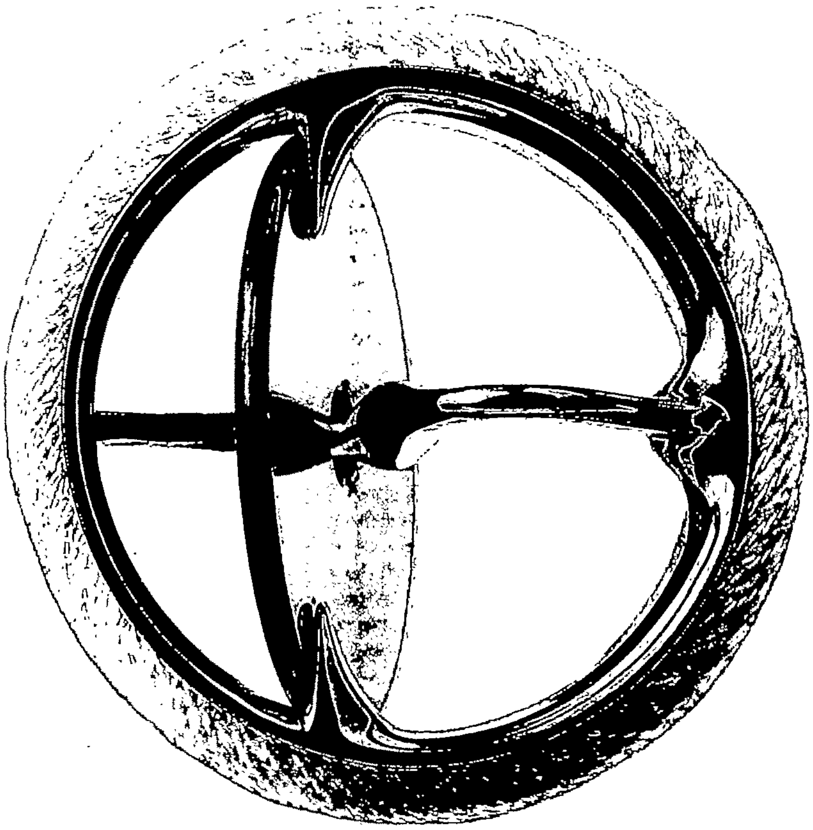

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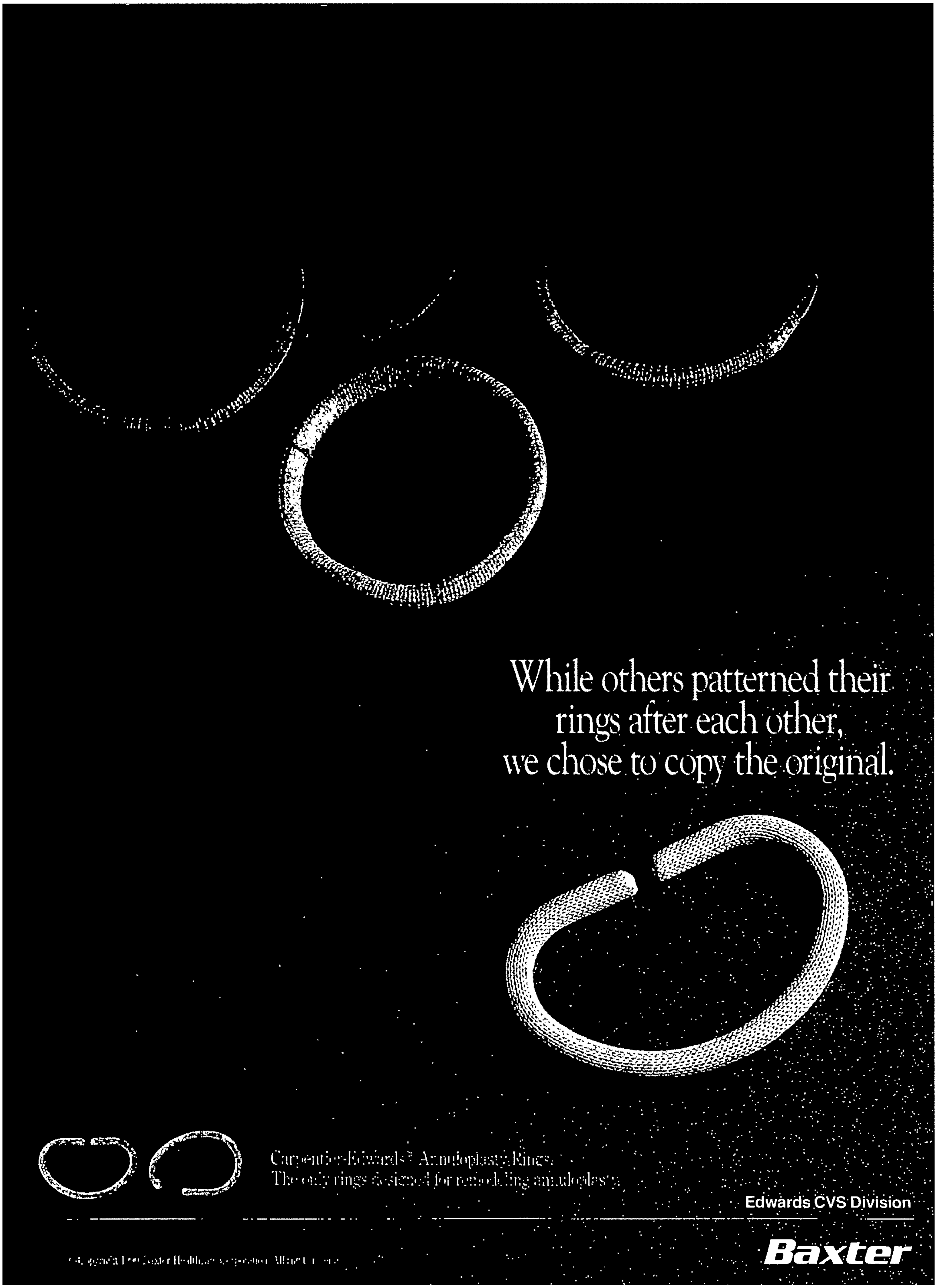
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Surgically Resected Lung Cancer in Young Adults

Kenji Sugio, MD, Teruyoshi Ishida, MD, Satoshi Kaneko, MD, Hideki Yokoyama, MD, and Keizo Sugimachi, MD

Department of Surgery II, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Twenty-two patients, 40 years old or younger, were surgically treated for lung cancer between 1974 and 1989. The male to female ratio was 1.2:1. Ten patients were symptomatic, with the average duration of symptoms being 3.6 months. There were 13 patients with adenocarcinoma and 9 patients with large cell carcinoma. In terms of postoperative stages, 5 patients were classified in stage I, 10 in stage IIIa, 5 in stage IIIb, and 2 in stage IV. Complete resection was performed in 14 patients, incomplete resection in 6, and exploratory thoracotomy in 2. The 3-year survival rate after complete resection was 66.2% in young patients, which was not significantly different from the 65.2% 3-year survival rate in older patients. There was no significant difference between the young and older groups according to histological cell type and TNM staging. In cases of incomplete resection or exploratory thoracotomy, 4 of 8 patients had been alive more than 2 years after operation. These results suggest that a long-term survival in the young patients is expected to be almost the same as that in the older patients after either complete resection or incomplete resection.

(Ann Thorac Surg 1992;53:127–31)

We [1, 2] reported previously that bronchogenic carcinoma occurs mainly in patients in the seventh decade of life, and there is no significant difference in long-term survival rate between the elderly group and the younger group. In contrast, lung cancer is rarely found in young patients, especially before 40 years of age. There are characteristic features in young patients with lung cancer that differ from those in older patients with lung cancer, that is, a relatively high incidence of female patients, a high incidence of adenocarcinoma, and a paucity of cases of squamous cell carcinoma [3–5]. Several reports suggest a poor prognosis [6, 7], whereas others suggest that there is no significant difference in long-term survival between young patients and older patients [3, 4]. However, a detailed analysis has not yet been performed on young patients who have undergone surgical resection.

In this context, we analyzed various clinical characteristics and the long-term survival rate in young patients surgically treated for lung cancer and compared the data with the findings in older patients treated during the same period.

Material and Methods

We retrospectively reviewed the medical records of 22 patients 40 years old or younger at the time of diagnosis with primary lung cancer surgically treated from 1974 to 1989 at the Department of Surgery II, Faculty of Medicine, Kyushu University. During this period, a total of 699 patients with lung cancer were surgically treated. This study excluded 9 patients who were histologically diagnosed as having a low-grade malignancy (carcinoid tumor, adenoid cystic carcinoma, and mucoepidermoid carcinoma). Thus, a total of 690 patients (524 male and 166 female) were analyzed.

Resected specimens were examined pathologically for tumor type and determination of the extent of lymph node spread. The pathological stages were determined according to the TNM classification revised in 1986 [8]. An incomplete resection means that there was macroscopic evidence of tumor or metastatic lymph node left behind, microscopic evidence of the tumor on the resected stump, or clinical evidence of distant metastasis.

Smoking history was based on the index of Brinkman and Coates [9], that is, the sum of the number of cigarettes smoked per day multiplied by the years of smoking.

The data from a total of 683 patients, excluding 7 patients who died within 30 days of operation, were statistically analyzed for the survival rates using the Kaplan-Meier estimated survival curves, and the significance of the difference was analyzed by the generalized Wilcoxon test. Results were considered to be significant if p was less than 0.05.

Results

Patient Profile

Of the 690 patients surgically treated, 22 (3.2%) were 40 years old or younger (Table 1). The age distribution was 23 to 40 years in the young group (average, 37.4 years) and 41 to 86 years in the control group (average, 63.7 years). The median age was 39 years in the young group and 64 years in the control group. The young group consisted of 12 men and 10 women (1.2:1). The control group of 668 patients consisted of 512 men and 156 women (3.3:1). This ratio was significantly different from the 1.2:1 ratio among the young group ($p < 0.05$).

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Table 1. Distribution of Patients According to Age and Histology[a]

Age (y)	Adenocarcinoma	Squamous Cell	Large Cell	Small Cell	Other	Total
21–30	1 (100)	. . .	. . .	. . .	. . .	1
31–40	12 (57.1)	. . .	9 (42.9)	. . .	. . .	21
41–50	22 (53.7)	7 (17.1)	10 (24.4)	1 (2.4)	1 (2.4)	41
51–60	106 (52.2)	62 (30.7)	16 (7.9)	11 (5.4)	7 (3.5)	202
61–70	127 (47.4)	112 (41.8)	18 (6.7)	7 (2.6)	4 (1.5)	268
71–80	65 (44.8)	58 (40.0)	11 (7.6)	8 (5.5)	3 (2.1)	145
81+	4 (33.3)	3 (25.0)	3 (25.0)	1 (8.3)	1 (8.3)	12
Total	337 (48.8)	242 (35.1)	67 (9.7)	28 (4.1)	16 (2.3)	690

[a] Numbers in parentheses are percentages.

The patients in the young age group are summarized in Table 2. Of the 22 patients, 10 were symptomatic; the most common symptoms were cough, hemosputum, and chest pain. The duration of symptoms ranged from less than 1 month to 7 months, and the average duration of symptoms was 3.6 months. The remaining 12 patients were asymptomatic: 10 patients were discovered by incidental routine chest roentgenograms, and 2 were discovered by chest roentgenograms done for the follow-up of other diseases. Three of the asymptomatic patients had a delay of from 9 to 18 months before the diagnosis of lung cancer was made because they had been treated as having pulmonary tuberculosis after the detection of their lesion on chest roentgenograms.

In the young group, 10 patients (45%) were smokers, but only 3 patients had a Brinkman index of greater than 800.

Histology and Stage of Disease

There were 13 patients with adenocarcinoma and 9 patients with large cell carcinoma. Table 1 shows the distribution of patients according to age and tumor type. No significant difference was observed in the frequency of patients with adenocarcinoma in each age decade. How-

Table 2. Lung Cancer in Young Adults

Age (y)	Sex	Symptoms	Brinkman Index	TNM	Cell Type	Operation	Type of Resection	Survival (mo)
38	F	(–)	0	T2N3M0	Adenocarcinoma	Lobectomy	Complete	24[a]
38	M	(–)	0	T1N2M0	Adenocarcinoma	Lobectomy	Complete	33[a]
40	M	Chest pain	0	T2N2M0	Large cell	Pneumonectomy	Complete	33[a]
39	F	Hemosputum	0	T2N0M0	Large cell	Lobectomy	Complete	138
40	F	Cough	0	T2N2M0	Large cell	Segmentectomy	Complete	7[a]
40	F	(–)	0	T4N1M1	Adenocarcinoma	Exploratory	Exploratory	27[a]
23	M	(–)	0	T1N0M0	Adenocarcinoma	Lobectomy	Complete	122
35	M	(–)	170	T2N2M0	Adenocarcinoma	Lobectomy	Incomplete	45[a]
34	F	Cough	0	T2N2M0	Large cell	Lobectomy	Complete	82
37	F	Chest pain	160	T3N2M0	Large cell	Lobectomy	Complete	82
39	M	Hemosputum	610	T4N2M0	Large cell	Exploratory	Exploratory	4[a]
35	M	Cough	50	T4N2M0	Large cell	Bilobectomy	Incomplete	13[a]
39	M	(–)	190	T4N2M0	Adenocarcinoma	Lobectomy	Incomplete	15[a]
40	F	(–)	0	T4N0M0	Adenocarcinoma	Lobectomy	Incomplete	30[a]
40	F	(–)	240	T2N2M0	Adenocarcinoma	Lobectomy	Complete	49
39	M	Chest pain	1000	T3N0M0	Adenocarcinoma	Partial	Incomplete	11[a]
32	M	Chest pain	800	T3N0M1	Large cell	Lobectomy	Incomplete	43
39	M	Hemosputum	0	T3N2M0	Large cell	Lobectomy	Complete	43
39	M	(–)	840	T2N0M0	Adenocarcinoma	Lobectomy	Complete	39
40	F	(–)	200	T1N0M0	Adenocarcinoma	Lobectomy	Complete	37
40	F	(–)	0	T1N2M0	Adenocarcinoma	Lobectomy	Complete	37[b]
36	M	(–)	0	T1N0M0	Adenocarcinoma	Lobectomy	Complete	22

[a] Dead of disease. [b] Alive with pulmonary metastasis.

Table 3. Distribution of Patients According to TNM Classification by Age Group[a]

Stage and TNM	Young Group	Control Group[b]	Total
Stage			
I	5 (23)[c]	312 (47)	317 (46)
II	0	46 (7)	46 (7)
IIIa	10 (45)[c]	163 (25)	173 (25)
IIIb	5 (23)	69 (10)	74 (11)
IV	2 (9)	38 (6)	40 (6)
TNM			
T1	5 (23)	206 (31)	211 (31)
T2	8 (36)	272 (41)	280 (41)
T3	4 (18)	74 (11)	78 (11)
T4	5 (23)	76 (11)	81 (12)
N0	8 (36)[c]	380 (57)	388 (56)
N1	1 (5)	70 (11)	71 (10)
N2	12 (55)[d]	170 (26)	182 (26)
N3	1 (5)	7 (1)	8 (1)
M0	20 (91)	590 (88)	610 (88)
M1	2 (9)	38 (6)	40 (6)

[a] Numbers in parentheses are percentages. [b] Forty patients were not classified. [c] Significance: $p < 0.05$. [d] $p < 0.01$ between the two groups.

ever, the high frequency of patients with squamous cell carcinoma more than 51 years of age was statistically significant ($p < 0.01$), and the high frequency of patients with large cell carcinoma less than 50 years of age was statistically significant ($p < 0.01$), which showed that squamous cell carcinoma was more common in older patients.

Patient staging was evaluated by age group (Table 3). In the young group, 5 patients had stage I disease, 10 had stage IIIa disease, 5 had stage IIIb disease, and 2 had stage IV disease. Significant differences were observed in these stages between the young group and control group. Significant differences were observed in the incidence of N0 and N2 disease between the young group and the control group. There were no significant differences between the young group and the control group with respect to type of resection (Table 4). In the young group, 14 patients (64%) had a complete resection, 6 patients (30%) had an incomplete resection, and 2 patients (9%) had an exploratory thoracotomy. The causes of incomplete resection or exploratory thoracotomy were malignant effusion proved by cytological examination (T4) in 3 patients, distant metastasis (intrapulmonary, brain) in 2 patients, marked invasion to chest wall (T3) in 1 patient, marked invasion to mediastinum (T4) in 1 patient, and unresectable mediastinal lymph node (N2) in 1 patient.

Table 4. Distribution of Patients According to Type of Resection by Age Group[a]

Type of Resection	Young Group	Control Group	Total
Complete	14 (64)	484 (72)	498 (72)
Incomplete	6 (27)	113 (17)	119 (17)
Exploratory	2 (9)	71 (11)	73 (11)

[a] Numbers in parentheses are percentages.

Survival

The 3-year survival rate after complete resection in the young group was 66.2% as compared with 65.2% for patients in the control group ($p = 0.3380$). Table 5 shows survival rates stratified according to histological type of the tumor or stage; there was no significant difference between the young group and the control group. Ten of 14 patients with complete resection are presently alive. All 5 patients with N0 disease are free of cancer; of 5 patients with N2 disease, 4 are free of cancer and only 1 has recurrent pulmonary metastasis. The 1-year and 3-year survival rates were 83.3% and 33.3% after incomplete resection in the young group.

Comment

Most previous studies [3-7, 10-13] on young patients with lung cancer have emphasized the relatively high incidence of female patients, the high incidence of smokers, the high incidence of adenocarcinoma and paucity of patients with squamous cell carcinoma, the high incidence of advanced stage of disease at the time of diagnosis, and the poorer prognosis in young patients than for the older patients with lung cancer. It has also been reported, however, that there is no significant difference in survival rates between young and older patients [3, 4, 11].

The male to female ratio in other reports has varied from 1.5:1 to 3.3:1 [4-7, 11, 13]. In this report, the male to female ratio was 1.2:1, whereas the ratio in the control group was 3.1:1. One of the reasons for the relative increase of female patients in this study is that there was no patients less than 40 years old with squamous cell carcinoma, because almost all patients with squamous cell carcinoma were male (male to female ratio, 11:1). Several studies have reported that smoking was an important factor in the occurrence of lung cancer in young people, and the reason for the relative increase in the number of women among the young patients is the increase of smokers among women [5, 11]. The histological type that has a close association with smoking is squamous cell carcinoma or undifferentiated carcinoma, not adenocarcinoma [14, 15]. However, only 3 of our patients were heavy smokers who had a Brinkman index greater than 800, and they were male. Therefore, the increase in smokers is not thought to be a reason for the increase of lung cancer in young female patients. Clearly, smoking is an important factor in occurrence of lung cancer for the general population, but it is also necessary to consider other environmental or genetic factors as previously suggested [16], especially in young patients with lung cancer.

In young patients, a high incidence of adenocarcinoma and undifferentiated carcinoma was found in some series.

Table 5. Survival Rates in Young and Control Group[a]

	Survival Rates (%)					
Variable	1 Year	2 Year	3 Year	4 Year	5 Year	p Value
Complete resection						
Young (14)	92.9	85.1	66.2	66.2	66.2	0.3380
Control (477)	90.8	75.6	65.2	59.4	53.7	
Adenocarcinoma						
Young (8)	100	85.7	64.3	64.3	64.3	0.3850
Control (237)	94.0	77.7	64.5	57.1	51.3	
Large cell carcinoma						
Young (6)	83.3	83.3	66.7	66.7	66.7	0.8561
Control (35)	79.0	75.6	75.6	70.6	70.6	
Stage I						
Young (5)	100	100	100	100	100	0.2189
Control (308)	95.6	86.5	77.8	72.3	68.0	
Stage III (IIIa, IIIb)						
Young (9)	88.9	77.8	51.9	51.9	51.9	0.1564
Control (126)	84.2	55.6	42.9	39.0	31.1	
Incomplete resection						
Young (6)	83.3	50.0	33.3	0	. . .	0.1615
Control (112)	50.0	35.6	23.1	19.4	17.9	
Exploratory thoracotomy						
Young (2)	50.0	50.0	0	. . .	. . .	0.7840
Control (69)	34.6	8.4	6.3	6.3	6.3	

[a] Numbers in parentheses are numbers of patients.

Neuman and associates [6] reported that the relative incidence of adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma was 37%, 8%, 24%, and 28%, respectively. DeCaro and Benfield [4] reported 49%, 17%, 29%, and 13%, respectively, and Pemberton and colleagues [13] reported 32%, 27%, 21%, and 13%, respectively. However, almost all cases of small cell carcinoma in these studies were not resected. We had no resected cases of small cell carcinoma, and the reason for this was thought to be their advanced stage at diagnosis. Our study showed that squamous cell carcinoma occurs mainly after the sixth decade of life. It seems reasonable to conclude that squamous cell carcinoma occurs less frequently in young people because of the requirement for longer exposure to carcinogens.

The high incidence of advanced stage of disease at diagnosis in young patients has been shown in this study, as has been commonly mentioned in many previous studies [5, 7, 13]. Of 12 asymptomatic patients, 5 had stage I disease and 7 had stage III disease, and 5 patients with stage I disease are still alive and well. In contrast, all symptomatic patients except 1 had stage III or IV disease. Although almost all reported cases of lung cancer in young patients were symptomatic [4, 5, 7, 13], our symptomatic cases were not as numerous. However, the fact that 7 of 12 asymptomatic cases had advanced stage with nodal involvement suggests that young people may have unknown factors that accelerate the growth and progression of lung cancer.

Several reports suggest that lung cancer in young patients is more rapidly fatal than that occurring in older patients [6, 7]. However, recently it was reported that there is no significant difference in the survival rates between young and older patients [3, 4]. DeCaro and Benfield [4] reported that young patients who were not operated on survived for a significantly shorter time than did older patients, but the 5-year survival rates of young patients were not different from older patients in the operative cases. Pemberton and associates [13] reported that the 1-year and 2-year survivals were 71% and 35% after curative resection and 79% and 28% after palliative resection. However, they did not show the survival rates of older patients. We found no significant difference in the survival rates between young and older patients. Therefore, it is reasonable to conclude that the prognosis of young patients with lung cancer was not different from older patients.

Currently, complete resection is the only modality to arrest the disease and is required to achieve a better prognosis in patients with lung cancer. Young patients have a good performance status to tolerate surgical treatment or adjuvant therapy at a lower risk, as previously reported [17]. Even in cases of incomplete resection or exploratory thoracotomy, 4 of 8 patients had been alive more than 2 years with chemotherapy or radiation therapy after operation. These results suggest that, despite the advanced stage of disease, better survival is expected in young adults.

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Left Ventricular Assistance Without Thoracotomy: Mediastinal and Transseptal Approaches to the Left Heart

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Two methods to cannulate the left atrium for initiating mechanical left ventricular circulatory assistance using a centrifugal pump were investigated in 25 sheep. A modified Dennis transatrial septal approach produced flow rates of 88.6 ± 14 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} through 21F catheters inserted during fluoroscopy through the jugular vein. In 8 animals the septal perforation was plugged after decannulation with a modified Rashkind umbrella plug. Fibroendothelial tissue covered the plug by 4 weeks. In 7 other animals, the septal defect was not plugged. The septal defect reached pinpoint size by 2 weeks and was completely closed by 4 weeks. In 10 sheep, the left atrium was cannulated from the neck through the mediastinum. Left ventricular assistance flow averaged 71.6 ± 14 mL $\cdot$ kg^{-1} $\cdot$ min^{-1}. Mean blood loss during 1 hour of left ventricular assistance was 47 mL. In 8 animals, the atrial perforation was plugged with a mean blood loss of 253 ± 194 mL. In 2 animals, the perforation was intentionally not plugged; mean blood loss was 700 mL. All animals survived. The modified Dennis transatrial method is recommended as a safe, expeditious, cost-effective method to implement left ventricular assistance without thoracotomy. The mediastinal approach, which is technically possible in humans, is more difficult but feasible. Left ventricular assistance has been proven to be the most effective way to rest the failing, ejecting left ventricle. Implementation without thoracotomy potentially expands applications of left ventricular assistance for temporary support of patients with severe manifestations of ischemic heart disease.

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Many causes of acute heart failure are reversible if the injured ventricle can be temporarily supported and adequate circulation maintained [1–9]. Although venoarterial bypass is easily and quickly implemented using peripheral cannulas [10–12], this bypass system does not adequately decompress the left heart [13, 14]. In 1960, Salisbury and associates [15] showed that left ventricular bypass was superior to venoarterial bypass for left ventricular failure. More recently, Bavaria and co-workers [16] demonstrated that venoarterial bypass actually increases wall stress in postischemic, failing hearts. In contrast, Ratcliffe and colleagues [17] have shown that left atrial to arterial bypass decreases circumferential wall stress, dramatically reduces end-systolic volume, and increases preload recruitable stroke work in the poorly contracting postischemic ventricle.

The need for thoracotomy is the primary disadvantage of temporary mechanical left ventricular circulatory assistance. In 1961, Dennis, Senning and colleagues [18, 19] blindly cannulated the left atrium in dogs and 7 patients from the jugular vein using a rigid metal cannula. Glassman and colleagues [20] revived this technique in 1975 using a long, flexible 26F catheter inserted from the femoral vein across the atrial septum in animals and 3 patients. There were no human survivors in either series.

Carlens [21] developed mediastinoscopy for staging lung carcinoma. From this approach, left atrial blood samples can be aspirated. In 1985, Seremitis [22] cannulated the left atrium of dogs from the mediastinum, and devised a double-balloon catheter to implement left heart bypass. However, he did not develop a means to decannulate, and this method has not been used clinically.

This study was designed to develop an expeditious, clinically applicable method to establish mechanical left ventricular assistance (LVA) without thoracotomy using the transseptal and mediastinal approaches.

Material and Methods

In pilot studies, techniques for cannulating the left atrium from the mediastinum and right internal jugular vein in sheep were developed (Fig 1). Human cadaver dissections were performed to confirm the feasibility of cannulating the left atrium from the mediastinum. A modified Rashkind patent ductus plug [23] was developed for closing left atrial puncture sites. Finally, animal studies were made to evaluate these cannulation and decannulation techniques and to determine maximal flow.

Twenty-five Dorsett sheep (38.0 ± 9.2 kg) were divided

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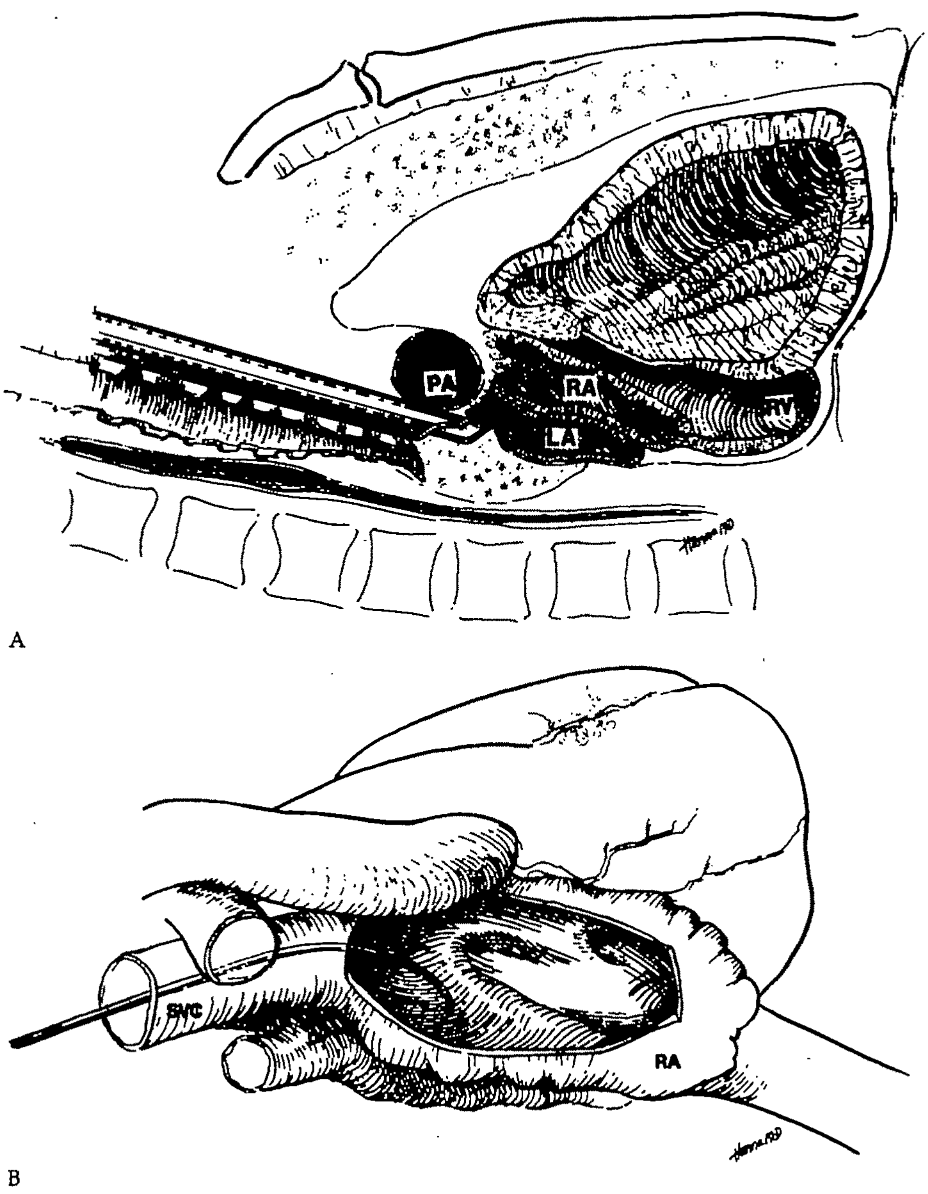

Fig 1. (A) Mediastinal approach to the posterior left atrium. (B) Transatrial approach before septal puncture. (LA = left atrium; PA = left pulmonary artery; PV = right pulmonary vein; RA = right atrium; SVC = superior vena cava.

into three groups. Group 1 (n = 10) animals were placed on LVA by the mediastinal approach. In group 2 (n = 8) sheep were placed on LVA by transseptal cannulation from the right jugular vein. The septum was closed with a Rashkind plug when the catheter was withdrawn. In group 3 (n = 7), the interatrial puncture site was not closed after decannulation.

All animals were premedicated with gentamycin (1.5 mg/kg intramuscularly), penicillin (600,000 U intramuscularly) and glycopyrolate (0.4 mg intravenously). Anesthesia was induced with thiopental sodium (25 mg/kg), and the animals were intubated in the supine position. Anesthesia was maintained with isoflurane inhalation (0.8% to 1.5%) during mechanical ventilation (Drager AV; Drager, Teleford, PA). The electrocardiogram and arterial pressure were monitored (BD Electrodyne ST419; Becton-Dickson, Sharon, MA). A fluoroscope (Mobile Fluoricon; General Electric, Milwaukee, WI) was placed in a cross-table lateral position. The necks were prepared and draped using sterile technique.

Group 1

A mediastinoscope was inserted along the pretracheal plane to the tracheal bifurcation (Fig 1). Tilting the scope upward at the tracheal bifurcation revealed the posterior wall of the left atrium. Before proceeding, the following structures were identified: (1) the right pulmonary veins entering the left atrium, (2) the pulmonary artery closely applied to the cranial edge of the left atrium with its right branches crossing over the trachea, and (3) the more proximal impression of the aorta. Under direct vision, a 31-cm, 16-gauge needle (BD-Yale, Rutherford, NJ) with a slightly curved tip was inserted into the posterior left atrium and bright red blood was withdrawn. After lidocaine bolus (3 mg/kg) and heparin (200 U/kg) bolus injection, a J-tip wire 3 mm in diameter and 150 cm in

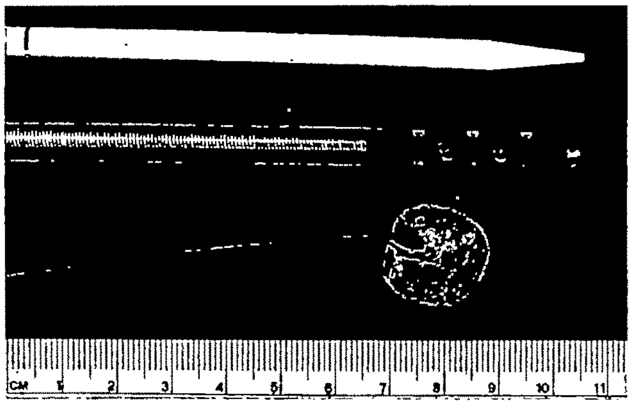

Fig 2. Modified Rashkind plug and 21F venous catheter with stylet.

length (Daig, Minnetonka, MN) was inserted into the needle and advanced under fluoroscopy into the left ventricle. A 21F, 50-cm, thin-walled, wire-reinforced venous cannula with a radiopaque tip and a firm plastic internal stylet (Medtronic–Biomedicus, Eden Prairie, MN) was advanced over the wire into the left atrium or ventricle. A 30-cm, 16F cannula (Medtronic–Biomedicus) was inserted into the right carotid artery.

Cannulas were connected to an LVA circuit consisting of 1/2-inch venous and 3/8-inch arterial polyvinyl tubing and a centrifugal flow pump (Medtronic–Biomedicus) with a built-in precalibrated electromagnetic flowmeter. The system was primed with 400 mL of hetastarch (Hespan; DuPont Pharmaceuticals, Wilmington, DE). Left ventricular assist was begun for 1 hour at the maximal flow rate attainable at less than 4,500 rpm. A long flexible suction catheter was placed in the mediastinum to monitor blood loss. Activated clotting time was maintained at greater than 350 seconds.

At the time of decannulation, heparin was fully reversed with protamine. An introducer was advanced down the venous cannula under fluoroscopy and the modified Rashkind plug was deployed immediately outside the cannula within the left atrium (Fig 2). The Rashkind plug was custom manufactured by Medtronics Inc. When folded, this device fit in a cannula with a 20F inner diameter. Unfolded, it had a strut diameter of 1.5 cm, with a total plug diameter of 1.8 cm. Full specifications are given in Appendix 1. Withdrawal of the cannula/introducer complex left the plug across the atrial puncture site. Manual tension was maintained until a long absorbable suture attached to the device was fixed to the trachea. The flexible mediastinal catheter was left in place until bleeding ceased. After bleeding stopped, the wound was irrigated and closed in layers. The awake animal was sent to the recovery room.

Group 2

In 8 animals, a 5-cm longitudinal sterile incision was made in the right side of the neck. Through a stab in the right internal jugular vein, a J wire was advanced under fluoroscopy into the inferior vena cava. A slightly curved 31-cm, 16-gauge needle (BD-Yale) with a rubber covering sheath was advanced along the wire into the inferior vena cava. Injection of 15 mL of 50% diatrizoate meglumine (Hypaque-76; Winthrop Pharmaceuticals, New York, NY) delineated the cavoatrial junction and the limbus. With the tip exposed and pointing directly posterior, the needle/sheath complex was slowly withdrawn. As the needle rode over the ridge of the limbus it "dropped" posteriorly (see Fig 1). At this point it was pushed across the septum. Fifteen milliliters of contrast medium were injected to confirm entrance into the left atrium. The J wire was inserted through the needle, and the 21F venous catheter and stylet were advanced across the septum, into the atrium, and if desired, into the left ventricle. The animal was connected to the LVA circuit as for group 1. After 1 hour, the animal was decannulated with the modified Rashkind plug device deployed in the left atrium. The device stay suture was brought out through the right jugular vein and attached to the nearby strap muscles.

Group 3

Seven animals were treated identically to group 2, but the septal defect was not closed.

All animals were killed at intervals, and careful postmortem examination was performed. Attention was paid to device location and coverage, and to signs of pericardial effusion or mediastinitis. The kidneys were finely sectioned for evidence of arterial emboli.

In 5 fresh sheep hearts, the intraatrial septum was punctured with the 21F cannula and stylet. The size and shape of the resulting defect were measured.

M numbers define pressure-flow relationships of catheters that vary in size and design [24]. Low M numbers describe catheters with high flows per unit pressure difference [24]. The M numbers of 19F and 21F venous catheters (Medtronic–Biomedicus) were measured in a water bath using a centrifugal pump. Flows were manually recorded with five timed 1-L collections at 10 different pump inlet pressures ranging from 0 to -100 mm Hg.

Results

Human cadaver dissections (Fig 3) demonstrated that cannulation of the superior wall of the left atrium is feasible in the human. During mediastinoscopy, a long 18-gauge straight needle enters the left atrium when passed over the origin of the left main bronchus–tracheal junction posterior to the left pulmonary artery, which is elevated anteriorly by the dissection and mediastinoscope.

Group 1 (Mediastinal)

All 10 animals were readily cannulated without complication. The venous cannula was placed in the left atrium in 4 animals and in the left ventricle in 6. Flow summaries are shown in Table 1. In 9 animals, there was less than 30 mL blood loss during the 1 hour of LVA. The tenth animal lost 200 mL of blood but completed the hour. Eight animals were decannulated and had the atrial defect plugged. The mean blood loss with this maneuver was 253 ± 194 mL. In the 2 animals without plugs, the mean loss was 700 mL.

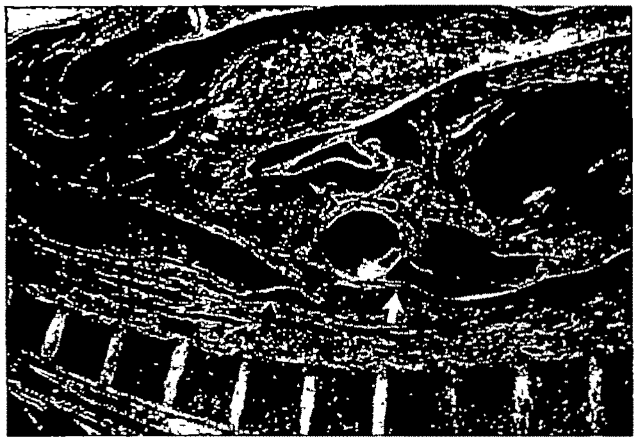

Fig 3. Midline sagittal section of a human cadaver. Left arrow is at the tracheal bifurcation, which is superior (cranial) to the large left main pulmonary artery. Upward tilting of the mediastinoscope lifts the left pulmonary artery near its origin to expose the superior wall of the left atrium (right arrow). Mediastinal fat and lymph nodes are posterior to the left pulmonary artery and are easily dissected away. (Dissection in collaboration with Dr Robert J. Johnson.)

The animals without plugs were sacrificed at 1 week, the others at 8 to 10 weeks. At postmortem examination, there was no evidence of tamponade, mediastinitis, embolic events, or endocardial injury in any animal. The plugs were well situated and covered with fibrous tissue.

Groups 2 and 3 (Transseptal)

Fifteen animals were readily cannulated without event. Flow rates during LVA are summarized in Table 1.

Left ventricular assistance was carried out without event for 1 hour. There was no substantial blood loss with decannulation. These animals were sacrificed at intervals from 3 hours to 8 weeks. Autopsies showed the plug covered with granulation tissue at 2 weeks and a complete fibrous coating at 4 weeks (Fig 4). Postmortem examination showed no evidence of tamponade, pericarditis, or endocardial or valve injury. In those animals without plugs, the defect was a pinpoint by 2 weeks and was completely healed by 4 weeks (see Fig 4). No animal had evidence of systemic emboli in kidney sections.

The animals placed on LVA by the transseptal approach had a slightly higher mean flow than the mediastinal group (88.6 ± 14 versus 71.6 ± 14 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $p = 0.014$). There was no significant difference in flow between those with catheters in the left atrium and those with catheters in the left ventricle ($p = 0.194$).

In five fresh cadaveric sheep hearts, the 21F catheter (7.1 mm) left a slit-like opening in the muscular septum after removal that measured 1.8 ± 0.2 × 5.2 ± 0.8 mm.

Flow characteristics of the two sample catheters are shown in Figure 5. The calculated M numbers were 2.67 and 2.81 for 21F and 19F venous cannulas, respectively.

Table 1. Catheter Position and Flow

Route	Catheter Position	Flow ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	n
Mediastinal			
	LV	79.5 ± 13	6
	LA	58.3 ± 15	4
	All	71.6 ± 14	
Transseptal			
	LV	89.9 ± 11	7
	LA	86.7 ± 18	8
	All	88.6 ± 14	
	All LV	85.6 ± 11	13
	All LA	76.1 ± 20	12

Comment

Left ventricular assistance rests the ejecting heart. No other mechanical circulatory assist system moves blood and also reduces the work of the heart [17]. However, the need for thoracotomy has largely limited clinical applications of LVA to postcardiotomy patients and those who are bridged to transplantation by modified versions of the artificial heart. Expanded applications require a method to implement LVA expeditiously and safely without thoracotomy. The dramatic physiologic benefits of LVA in the ejecting failing heart compel greater efforts to broaden clinical use.

Zwart and associates [26] introduced transaortic LVA in 1966. The recently introduced Nimbus Hemopump (Nimbus Medical, Inc, Rancho Cordova, CA) also aspirates blood from an intraventricular catheter and ejects it into the ascending or descending aorta. The pump itself resides within the aorta and is driven by a transarterial and transcutaneous cable and external motor. This novel device may achieve wide clinical application, but currently it has several limitations. The intraaortic screw pump is pressure sensitive and flow decreases as pressure rises [27]. Cable torque and reliability are problems with the pump operating at high speeds [27, 28]. Insertion of the 7-mm-diameter pump and stiff catheter requires access to the aorta or a large artery [27–29]. Injury to the aortic valve, induction of arrhythmias, and perforation of the ventricle, particularly if a fresh infarct is present, are also important concerns.

Modernization of the Dennis technique provides a safe, expeditious means to implement LVA. We recommend the cervical approach, which permits insertion of shorter, larger-diameter catheters than the femoral approach. From the neck, the angle of entry into the left atrium is less acute and may allow better flow. The catheter can also be easily advanced into the left ventricle if desired. The catheters used in this study are substantially smaller (21F versus 26F) than those used by Glassman and co-workers [20] but still attained excellent flow without excessive pump speed (always less than 4,500 rpm). Catheter flow is influenced by the ratio of catheter to vessel diameters [30] and the flow characteristics of the catheter as indicated by the M number [24]. The cervical approach using

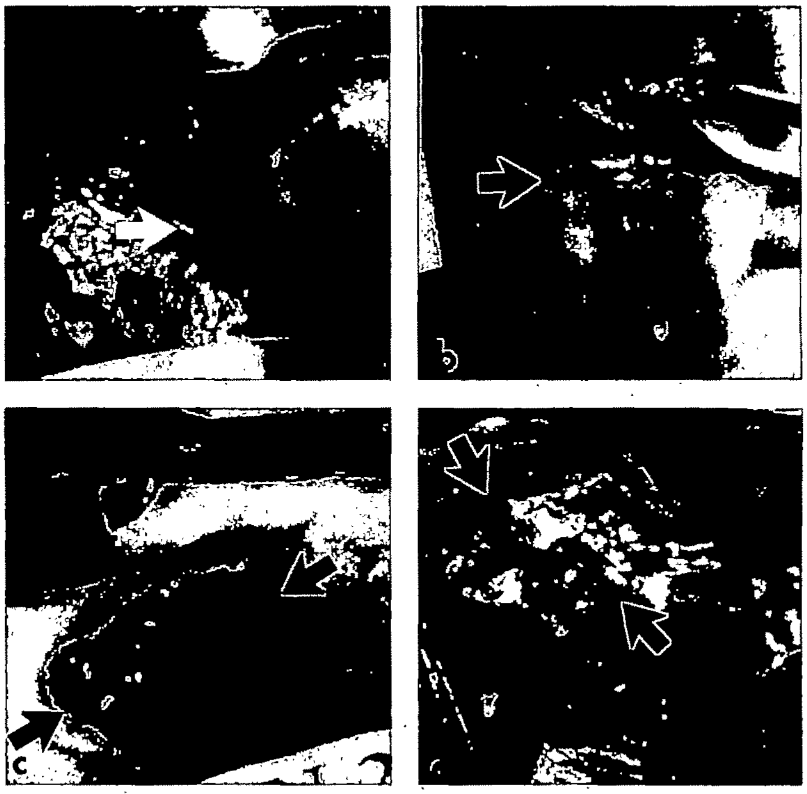

Fig 4. (a, b) Septal puncture sites (arrows) *from the right atrium at 2 and 4 weeks, respectively. (c, d) Defect with Rashkind plug in place at 2 and 4 weeks from left atrium.* (FO = *foramen ovale;* IVC = *inferior vena cava;* SVC = *superior vena cava.)*

the Medtronic-Biomedicus catheter permits high flow and creates small interatrial punctures.

The Dennis transseptal method requires fluoroscopy, but it uses existing technology and equipment and requires less expertise than a balloon mitral valvuloplasty. The LVA system is readily available in hospitals that perform catheterizations and open heart operations, and does not require additional personnel to operate. The centrifugal pump is reliable and has low heparin requirements. The availability of a plug to close the septal perforation is a backup option for patients who do not tolerate temporary left-to-right shunts. Experience with balloon mitral valvuloplasty suggests that few patients will need plugs [31, 32].

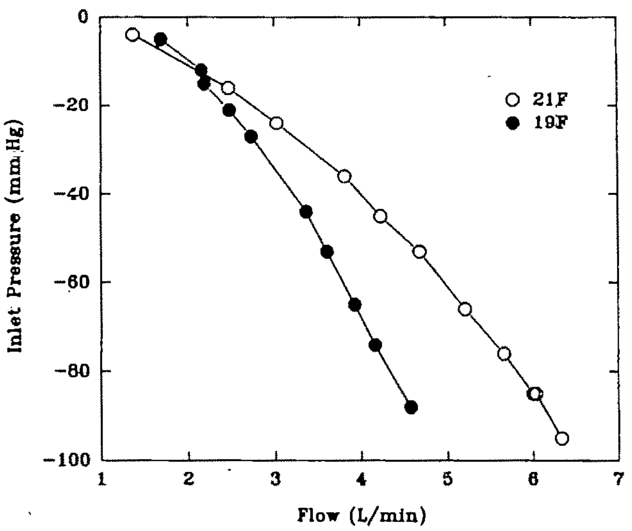

Fig 5. Flow characteristics of 19F and 21F Medtronic–Biomedicus venous catheters at varying inlet pressures.

The mediastinal approach is less attractive than the transseptal method but may occasionally be used for special circumstances. General anesthesia is required, and the operator must be thoroughly familiar with mediastinoscopy. Perhaps owing to catheter positioning, this technique achieves slightly lower flows than the transseptal method in sheep. Plugging the hole after decannulation is mandatory but not difficult.

Several exciting potential applications of LVA are introduced by the avoidance of thoracotomy. In patients with cardiogenic shock after acute myocardial infarction [6], LVA can stabilize the circulation, unload the left ventricle, and prevent ischemic damage to other organs while thrombolysis, cardiac catheterization, angioplasty, or emergency revascularization is performed [33–35]. There is evidence that LVA may actually reduce the size of the infarct [36–39], and by resting the ejecting ventricle, LVA may prevent infarct expansion or new ischemia in the distribution of a second partially obstructed coronary artery [40]. By maintaining ventricular ejection, LVA reduces the possibility of intraventricular clot. Acute infarctions cause severe dysfunction in adjacent, nonischemic myocardium [41] by a poorly understood mechanism that may be related to stretch injury and myocardial creep

[42]. Left ventricular assistance may accelerate recovery from both myocardial creep and reversible ischemia or stunning [43]. Finally, by reducing ventricular end-diastolic and end-systolic volumes and regional wall stresses, LVA may favorably alter ventricular remodeling and prevent ventricular rupture and aneurysm formation after acute infarction. Although the efficacy of LVA in these latter applications remains to be demonstrated, avoidance of thoracotomy and the inherent simplicity, safety, and cost-effectiveness of the technique provide new opportunities to preserve myocardial mass and function in patients with severe manifestations of ischemic heart disease.

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Appendix 1

The umbrella frame is manufactured of 0.010 304v stainless steel wire. It is attached to a 130-cm No. 1 polyglactin suture (Ethicon, Somerville, NJ). This is secured with 4-0 polypropylene (Ethicon). The 1.2-mm-thick, 1.8-cm-diameter foam disc is composed of TDI-based polyether polyurethane slabstock foam 2.5 lb/ft^3 with ILD 25 lb at 25% deflection. It is coated on its interior surface with Estane 83A polyether polyurethane (B.F. Goodrich). It differs from the Rashkind plug [23] in that it has four struts instead of three, and the foam is coated to render it impermeable for acute hemostasis in potentially coagulopathic settings. It is also attached to an absorbable traction suture to maintain positioning until healing occurs.

The introducer is designed to reach the tip of the catheter and to release the preloaded plug by advancing a wire stylet. It fits down a 19F (inner diameter) or larger catheter.

Recurrent Intravenous Leiomyomatosis With Cardiac Extension

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A case of recurrent intravenous leiomyomatosis with cardiac extension and a temporally extended presentation is described. Complete excision was achieved employing simultaneous sternotomy and laparotomy and deep hypothermia with circulatory arrest. Coronary revascularization was performed concomitantly with complete tumor resection. Diagnostic, operative, and pathologic considerations are reviewed and a preferred surgical approach discussed.

(Ann Thorac Surg 1992;53:139–41)

Intravenous leiomyomatosis of uterine origin has rarely been reported to involve cardiac extension [1–9]. Multiple unusual features of the present case warrant its presentation as well as a review of this uncommon clinical entity with attention to diagnostic and therapeutic options.

The patient is a 57-year-old gravida 3, para 3, white woman who had a 5-day history of constant right lower quadrant abdominal pain without associated symptoms or suggestion of embolic phenomena. The medical history was significant for subtotal hysterectomy with bilateral salpingo-oophorectomy performed 10 years before admission for a large pelvic leiomyoma and wedge resection of the right lower lobe of the lung 7 years later for multiple pulmonary nodules. History was also notable for deep venous thrombosis after saphenous vein stripping complicated by pulmonary embolus. Physical examination revealed a blood pressure of 140/70 mm Hg, pulse rate of 70/min and regular, absent jugular venous distention, and clear lungs. The cardiac examination was normal. The abdomen was tender in the right lower quadrant initially, but this resolved spontaneously. No abdominal masses or organomegaly were present. Rectal and pelvic examinations were unremarkable. The extremities were without edema. Routine laboratory values were normal with the exception of elevations in levels of aspartate aminotransferase (87 U/L; normal, 10 to 50 U/L) and alanine aminotransferase (108 U/L; normal, 10 to 50 U/L). The electrocardiogram showed normal sinus rhythm with left ventricular hypertrophy and strain. Radiographs of the chest showed a surgical staple line from the previous pulmonary resection without acute processes.

Ultrasound examination of the abdomen demonstrated a mass in the inferior vena cava (IVC) beginning at the level of the left renal vein extending proximally into the right atrium but not protruding through the tricuspid valve orifice. Computed tomography revealed the origin of the mass to be in the pelvis. Inferior venacavography was confirmatory of these findings. Cardiac catheterization showed normal left ventricular function with a 70% stenosis of the proximal left anterior descending coronary artery, a 40% stenosis of the midportion of the right coronary artery, and a 70% stenosis of the first obtuse marginal branch of the left circumflex vessel.

Median sternotomy was performed simultaneously with exploratory laparotomy through a midline incision. After isolation of the pelvic mass and identification of its junction with the IVC, the patient was systemically heparinized. Arterial perfusion was through the ascending aorta. The superior vena cava was cannulated directly, and a second venous cannula was placed in the right atrium through the right atrial appendage. Venous return proved quite satisfactory except when the heart was elevated for examination of the posterior left ventricle. Total cardiopulmonary bypass was then initiated and two reversed saphenous vein segments anastomosed end-to-side to a partially excluded segment of the aorta. The patient was cooled to a minimum temperature of 20°C. After aortic cross-clamping and infusion of cold blood cardioplegia, the saphenous vein grafts were anastomosed end-to-side to the left anterior descending and obtuse marginal branch of the left circumflex coronary arteries, respectively. Cardiopulmonary bypass was then terminated and the patient exsanguinated. The intracaval portion of the mass was divided and partly excised in continuity with a portion of the anterior wall of the IVC that incorporated the orifice of the ovarian vein. This allowed delivery of the remaining intracaval portion through a transverse right atriotomy without difficulty. Cardiopulmonary bypass was reinstituted after 16 minutes of circulatory arrest. The aortic cross-clamp was removed after a total ischemic time of 48 minutes, and the

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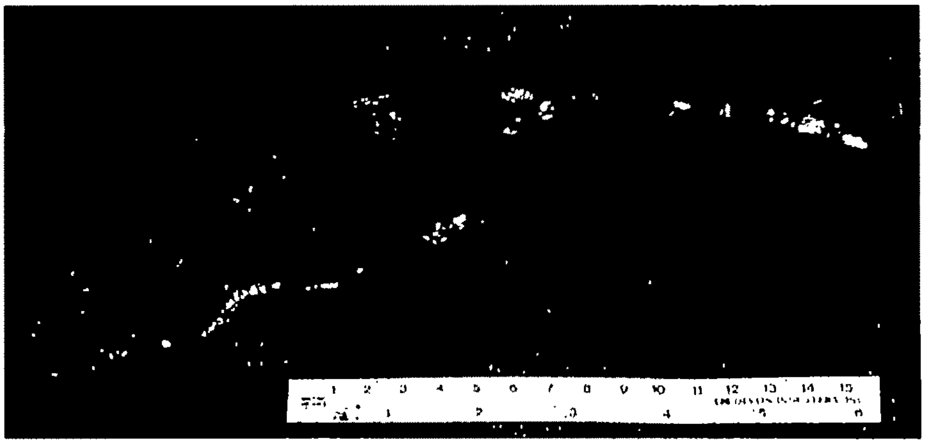

Fig 1. Examination of the surgical specimen demonstrated the whitish dumbbell-shaped intraluminal component as well as the extracaval component, which was encased by vein wall. The point of connection can be seen in the photograph and was also the site of attachment to the wall of the inferior vena cava.

operation was completed in routine fashion. The patient's postoperative course was without complications.

At operation, the tumor was found to originate in the pelvis in an ovarian vein and ascend parallel to the IVC. At the level of the left renal vein it grew into the IVC and extended intraluminally to the right atrium. The only attachment of the tumor to the IVC was at the level of the left renal vein. The cavoatrial portion of the tumor measured approximately 15 cm in length and 3 to 4 cm in greatest diameter (Fig 1). The extracaval portion of the tumor was surrounded by vein wall. Histologic evaluation indicated that the tumor was a leiomyoma of cellular type without atypia or mitotic figures. The pathology of the original pelvic tumor and the previously resected pulmonary nodules was reviewed. All were leiomyomas with essentially identical histologic features. No mitotic figures were evident in the sections of any of the three tumors, consistent with a "benign" histology.

Comment

The unusual features of this case include: (1) the long delay (10 years) from the performance of subtotal hysterectomy to presentation of caval and cardiac extension; (2) the intervening excision of presumed embolic spread of tumor to the lungs 7 years after removal of the pelvic primary tumor; (3) the atypical presentation without evidence of right heart failure; (4) complete excision with simultaneous sternotomy and laparotomy employing deep hypothermia and circulatory arrest; and (5) performance of a concomitant procedure (coronary artery bypass) at the time of complete tumor resection.

Intravenous leiomyomatosis with cardiac extension has been reported in fewer than 30 cases [1–9]. All reported patients are female, and the cases universally associated with leiomyomas of uterine origin [1]. The majority of patients are white, are premenopausal, and have had previous pregnancies [1]. Intravenous spread to the IVC is usually through iliac or ovarian veins, as in this case. Histologically this tumor must be differentiated from leiomyosarcoma. This distinction is based on the minimal or absent mitotic activity present on section of leiomyomas [10]. Universal agreement as to precise terminology in this area does not exist. It should be recognized that some pathologists would consider the original uterine lesion in our patient to be, by definition, a low-grade leiomyosarcoma, despite its histologic appearance, because it "metastasized" [11]. Intravenous leiomyomatosis usually follows a benign course if amenable to complete excision [2, 3]. Cytoplasmic estradiol and progesterone receptors have been demonstrated in the right atrial component of such tumors, suggesting hormonal influence in their development [2, 3]. This has implications for the use of antiestrogen hormonal therapy in cases of incomplete resection [2, 3].

Substantial time intervals have previously been reported between removal of the uterine primary and subsequent leiomyomas [4, 5, 11]. However, the intervals from the time of subtotal hysterectomy in this patient to pulmonary resection (7 years) and to presentation of the cavoatrial mass (10 years) are among the longest recorded to date. Although the tumor in the vena cava and atrium presumably resulted from direct extension of residual tumor left at the time of subtotal hysterectomy through an ovarian vein to the IVC, the previously resected pulmonary nodules are more likely explained by hematogenous spread or embolization of tumor.

Ultrasonography and echocardiography are the cornerstones of diagnosis. However, in the present case, computed tomography suggested the cause of the tumor by demonstrating its origin in the pelvis. It was the only diagnostic modality employed that showed the complete extent of the tumor. Inferior venacavography did not substantially contribute to the information provided by computed tomography. Cardiac catheterization is not required for diagnosis. However, given that the surgical approach to cardiac extension of such tumors usually entails cardiopulmonary bypass, it is indicated and recommended in selected patients to detect coexisting pathology. Our patient was such an example. She was a middle-aged smoker and proved to have serious coronary occlusive disease amenable to concomitant surgical intervention. Complete surgical excision is the therapy of choice for intravenous leiomyomatosis. The majority of cases reported previously used a staged approach involving resection of the abdominal/pelvic and intrathoracic components in two separate operations. Although both a nonstaged approach [6] and circulatory arrest [7, 8] have been employed, our report is unusual in that a concomitant procedure was performed at the time of complete tumor excision. Procedures including tricuspid annuloplasty [5] and mitral valve replacement with coronary revascularization [9] have previously been performed at the time of partial tumor excision. Coronary artery bypass was performed uneventfully in our patient, underscoring the importance of preoperative cardiac catheterization in selected patients.

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Esophagobronchial Fistula Associated With Corrosive Stricture of the Esophagus

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Two cases of esophagobronchial fistula that developed as a late complication of corrosive injury to the esophagus associated with stricture are described, stressing the need for awareness of this rare entity and specificities of management.

(Ann Thorac Surg 1992;53:142–3)

Benign esophagorespiratory fistulas are most commonly the consequence of trauma or of an inflamed esophageal diverticula, but occasionally they may also result from an extensive corrosive burn of the esophagus [1]. It has been stated that fistula develops either as an early complication of acute corrosive esophagitis, particularly in patients treated with large doses of steroids, or as a complication of later dilation of the resulting stricture [2, 3]. From January 1964 to January 1991, we treated 223 patients for corrosive stricture of the esophagus. Among them, we detected 3 cases of established esophagobronchial fistula that developed as a late complication of corrosive injury to the esophagus in patients who had not undergone treatment either with steroids or dilations. The first patient has been recently reported [1]; here, we present 2 new cases of this rare lesion.

Case Reports

Patient 1

A 57-year-old woman attempted suicide by massive ingestion of glacial acetic acid. Severe stricture developed at the midesophagus. Gastrostomy was initially constructed to provide enteral nutrition, and 6 months later she was readmitted for esophageal reconstruction. At admission, she suffered respiratory infection and complained of a recurrent cough after drinking liquids that had started 1 week before admission. A chest roentgenogram showed pneumonic involvement of the right middle lobe. Barium swallow revealed a fistulous connection that had not been previously demonstrated between the midthoracic esophagus just above the uppermost level of the stricture and the right main bronchus (Fig 1). After antibiotic therapy for pulmonary infection, operation was performed through a right thoracotomy. The fistula was divided and the bronchial defect was oversewn; the scarred esophagus

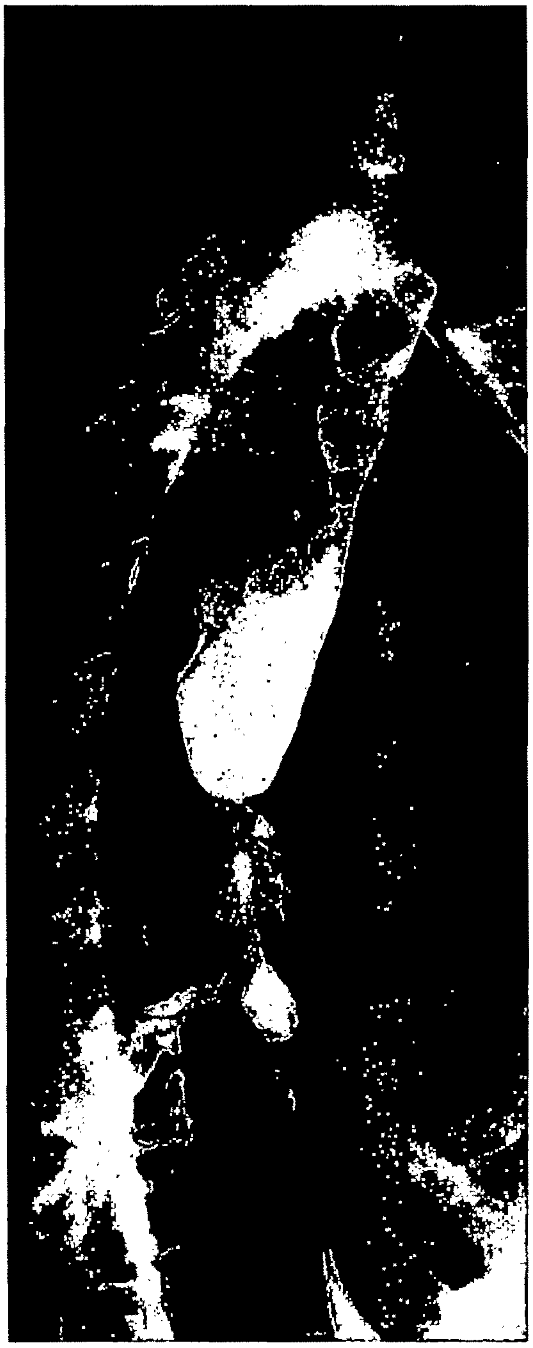

Fig 1. Esophagogram 6 months after corrosive ingestion showing stricture of distal third of the esophagus and a fistulous communication with the right main bronchus.

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indicated esophagectomy with a cervical esophagostomy. She made a rapid recovery and 2 months later underwent reconstruction by a substernal isoperistaltic coloplasty. The postoperative course was unremarkable, and she remains well.

Patient 2

A 17-year-old boy was referred with complete dysphagia and a history of recent inadvertent ingestion of a few sips of unknown liquid cleaner. Barium swallow showed only an extensive stricture at the upper thoracic esophagus. A long and filiform stricture precluded dilation, and a feeding gastrostomy was constructed. Five months later he had no symptoms and was readmitted for definitive reconstruction. Control barium swallow, however, demonstrated a fistulous connection between the strictured esophagus and the left main bronchus. Through a right thoracotomy, the fistula was divided and the bronchial defect was oversewn; the scarred esophagus indicated esophagectomy and a cervical esophagostomy. Three months later the patient underwent an uneventful substernal isoperistaltic coloplasty, and he remains well.

Comment

Esophagorespiratory fistula may also arise as a late complication of corrosive injury to the esophagus associated with a stricture. This is a rare lesion which, in our experience, developed in 1.5% of patients with postcorrosive stricture of the esophagus. It seems that those with stricture at the midesophagus are at a higher risk of the development of fistula to one of the main bronchi. The lesion may be attributed to persisting inflammation within the esophageal wall, concomitant involvement of carinal and peribronchial lymph nodes, and, finally, erosion of the adjacent membranous bronchial wall. An additional factor may be distal esophageal obstruction, which makes the situation similar to those with esophageal atresia. It seems that the process that results in fistula formation takes a few months. Awareness is needed that symptoms may be absent when the esophageal fistulous opening is in the strictured segment or while gastrostomy is used for nutrition. A complete evaluation before definitive surgical repair of postcorrosive stricture is mandatory as unrecognized fistula may make it hazardous. Surgical repair is indicated once the diagnosis has been established. Repair in these patients, however, differs from the standard repair of esophagorespiratory fistulas. It consists of division of the fistula and suture of the respiratory defect; the damaged esophagus precludes direct repair and indicates esophagectomy. We recommend colon interposition for esophageal replacement [4]. The shortest (mediastinal) route for the transplant should be avoided in these patients because of mediastinal infection, and the substernal route should be used. We consider this complex repair safer to perform as a two-stage procedure.

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Unsuspected Metastatic Choriocarcinoma Presenting as Unilateral Spontaneous Pneumothorax

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Spontaneous pneumothoraces are usually caused by subpleural apical blebs but may also be secondary to metastasis to the lung. We present the case of a 20-year-old woman with spontaneous pneumothorax secondary to choriocarcinoma metastatic to the lung.

(Ann Thorac Surg 1992;53:144–5)

Spontaneous pneumothorax in young adults is relatively common. The overall incident is estimated at 5 to 10 per 100,000 per year and as high as 1 in 500 young men. Pneumothorax in this age group is usually the result of the rupture of an apical lung bleb but may also be secondary to underlying pulmonary pathology such as emphysema, tuberculosis, eosinophilic granuloma, and rarely lung neoplasm (primary and secondary). The latter group is quite uncommon. In a review of 1,143 patients with spontaneous pneumothorax, 10 cases were attributed to metastases to lung. Five of these were secondary to metastatic sarcoma [1].

Although choriocarcinoma frequently metastasizes to the lung, in the English-language literature there is only 1 reported case of bilateral spontaneous pneumothorax in a patient with choriocarcinoma, but lung metastases was not proven [2]. We report a case of metastatic choriocarcinoma to the lung presenting as a spontaneous pneumothorax.

A 20-year-old woman was seen at a community hospital with sudden shortness of breath and chest pain. She was found to have a left spontaneous pneumothorax. A chest tube was inserted, but an air leak persisted for 3 weeks. Attempted clamping of the chest tube resulted in collapse of the lung. She was referred to our institution. On arrival she was in no distress and her physical examination was essentially normal except for an air leak from her chest tube. The chest tube was soon able to be removed, with the lung reexpanded, and she was discharged.

She returned 2 days later with left-sided chest pain and shortness of breath. A chest roentgenogram showed recurrence of her left pneumothorax. A Heimlich valve was inserted with relief of symptoms and complete expansion of her lung. As this was her second pneumothorax in a short period it was decided to proceed with a left transaxillary thoracotomy and exploration. This was performed the following day. A bulla was found at the apex and was excised. Mechanical pleurodesis of the apex of the pleura was then performed. Postoperatively she did well, and after a few days, the chest tube was removed as there was no air leak and minimal drainage. The following day a chest roentgenogram showed a basal pneumothorax. Over the next few days it continued to increase in size, but with the apex well adherent to the chest wall.

The decision was then made to perform a formal left thoracotomy to explore for further bullae. At thoracotomy, air could be seen leaking from the fissure. On the undersurface of the left upper lobe a 2-mm yellowish nodule was found from which air could be seen bubbling out. This was excised with a wedge excision. Postoperatively the lung remained well expanded. On the specimen of the lung a 1 × 0.6 × 0.3-cm nodule was visible. Microscopic examination revealed the nodule to be subpleural, containing necrotic cells and a few islands of viable cells. These cells consisted of large, highly atypical cells with abundant cytoplasm and irregular nuclei. They stained positively for cytokeratin and β-human chorionic gonadotropin. These features are consistent with a choriocarcinoma. Thus the diagnosis of metastatic choriocarcinoma to the left upper lobe was made.

With this information, the patient was further questioned and admitted to being pregnant 5 years earlier and having a therapeutic abortion. At the time of her dilation and curettage she was told that she had a "grapelike lesion" that may reoccur. The pathologic slides from material obtained were reviewed and showed multiple edematous avascular chorionic villi covered by trophoblast, consistent with hydatidiform mole. Subsequent full metastatic work-up including β-human chorionic gonadotropin analysis and computed tomographic scan of the head, chest, and abdomen has failed to demonstrate other sites of metastases.

Comment

The lung is a frequent site for metastasis from malignant neoplasms presenting as a diffuse infiltrate, a single mass, multiple nodules, or pleural effusion. Pneumothorax is an unusual presentation of lung metastasis and was first described by de Barrin in 1937 [3]. Tumors associated with pneumothorax include sarcoma; Ewing's sarcoma; teratoma; Wilm's tumor; malignant melanoma; carcinoma of

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the cervix, pancreas, or kidney; leiomyosarcoma of the uterus; and, most commonly, osteogenic sarcoma. Two mechanisms have been speculated for pneumothorax secondary to cancer. The first consists of tumor emboli in a subpleural position with infarction of the lung, necrosis, and air leakage [4]. The second mechanism involves tumor growth causing obstruction as a ball-valve effect, resulting in the disruption of the alveoli and leaking of air, which dissects into the subpleural space and forms blebs that rupture [5].

The only other reported case of choriocarcinoma with bilateral pneumothoraces was in a young woman who had a pelvic mass that was found to be a primary nongestational choriocarcinoma of the ovary. She died postoperatively with respiratory failure and hypotension. Unfortunately an autopsy was not performed; thus it is unclear if she had lung metastasis [2].

Hydatidiform mole is considered a benign disorder, but choriocarcinoma develops in 1% of these patients. Choriocarcinoma is a rare, highly malignant tumor and frequently metastasizes hematogenously to the lung, vagina, liver, and brain [6].

Spontaneous pneumothorax is relatively frequent in young patients and is usually primary in nature and due to rupture of an apical subpleural bleb. However, one should keep in mind the possibility of pneumothorax occurring secondary to a lung metastasis.

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Complete Thoracic Ectopia Cordis With Double-Outlet Right Ventricle: Neonatal Repair

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A case of total thoracic ectopia cordis with double-outlet right ventricle and ventricular septal defect is presented. Prenatal diagnosis allowed single-stage correction immediately after birth. This approach proved to be technically feasible. Death occurred on the twelfth postoperative day owing to sepsis unrelated to the repair.

(Ann Thorac Surg 1992;53:146–7)

Ectopia cordis is a very rare congenital defect commonly associated with intracardiac defects and can be seen in either partial or complete forms [1–6]. Survival has been difficult to achieve in the latter condition. We report a case of complete thoracic ectopia cordis with double-outlet right ventricle and ventricular septal defect in which a one-stage correction was attempted immediately after birth.

A 38-year-old woman was referred after a routine second trimester ultrasound (17 weeks' gestation) revealed ectopia cordis. Further serial ultrasound examinations demonstrated a ventricular septal defect, but the great vessel relationships were not clear. A one-stage correction was planned, and because of developing hydrops the fetus was delivered by classic cesarean section at 36 weeks gestation in an adjacent operating room. There was a tear in the epicardium across the right atrium and extending onto the right ventricle. The heart was covered with sterile plastic and the infant resuscitated. The entire heart was protruding through a large defect involving the front of the chest wall and through which both lungs were also partially protruding (Fig 1). Sterile echocardiography demonstrated double-outlet right ventricle with ventricular septal defect. A persistent left superior vena cava was visible. Pressure lines were inserted and the patient was redraped and a one-stage repair embarked upon.

A midline incision was made up into the neck above the thoracic defect and down into the abdomen. There was a single cartilaginous bar crossing the midline inferiorly but no xiphisternum. This bar continued in a horseshoe fashion, and the front ends of the ribs and clavicles were attached to it. There was no sternum superiorly. Cardiopulmonary bypass was instituted using a single venous cannula with core cooling to 16°C. During cooling, the ductus was divided and the lungs fully mobilized from the edges of the defect in the thoracic wall. The diaphragm was detached anteriorly from the inferior cartilaginous bar, which was then excised, allowing the liver to move posteriorly. After circulatory arrest a right atriotomy was performed. A noncommitted ventricular septal defect was visualized in association with double-outlet right ventricle, and so a long Dacron patch was inserted to connect the left ventricle to the aorta.

During rewarming, thoracic expansion was performed and involved the following steps: (1) The anterior diaphragm was divided down to and to the right of an anteriorly placed inferior vena cava to allow the inferior vena cava to settle posteriorly when the heart was placed in situ. (2) An incision was made in the pleura in both costophrenic angles for the complete circumference to allow the diaphragm to move down about 0.75 cm and increase the thoracic cavity on each side. (3) Right-sided multiple rib slide was performed after the intercostal spaces had been exposed. Each rib was split longitudinally for 2 cm and half transected at medial and lateral ends. A rib slide was then carried out with a 4-mm overlap, moving the ventricle cartilage bar 1.5 cm toward the midline. (4) On the left side the ribs were transected in a staggered fashion, allowing the left vertical cartilage bar to move 0.5 cm toward the midline.

The heart was inserted inside the thoracic cavity with the apex to the left, and the patient was weaned from bypass with satisfactory hemodynamics. The vertical cartilage bars were sutured together followed by direct skin closure. Peak lung inflation pressure was 32 mm Hg. Over the next 36 hours the circulation deteriorated. Sutures to the midportion of the sternal bars were removed, and the elliptical gap was closed with a thin Gore-Tex patch. The skin edges were reclosed. Subsequently the child's condition steadily improved, and by the ninth postoperative day he had stable hemodynamics with satisfactory lung fields radiologically (Fig 2) and a peak lung inflation pressure of 21 mm Hg. One day later hemodynamic collapse occurred with a clinical picture of sepsis (fever, low blood pressure, dilated periphery, rising white blood cell count [10 to 32 × 10^9/L] and falling platelet count). Use of antibiotics and increased inotropes led to some clinical improvement, but the general course was downhill with death on the twelfth postoperative day. Autopsy confirmed the diagnosis with an associated moderately hypoplastic left ventricle and mitral valve.

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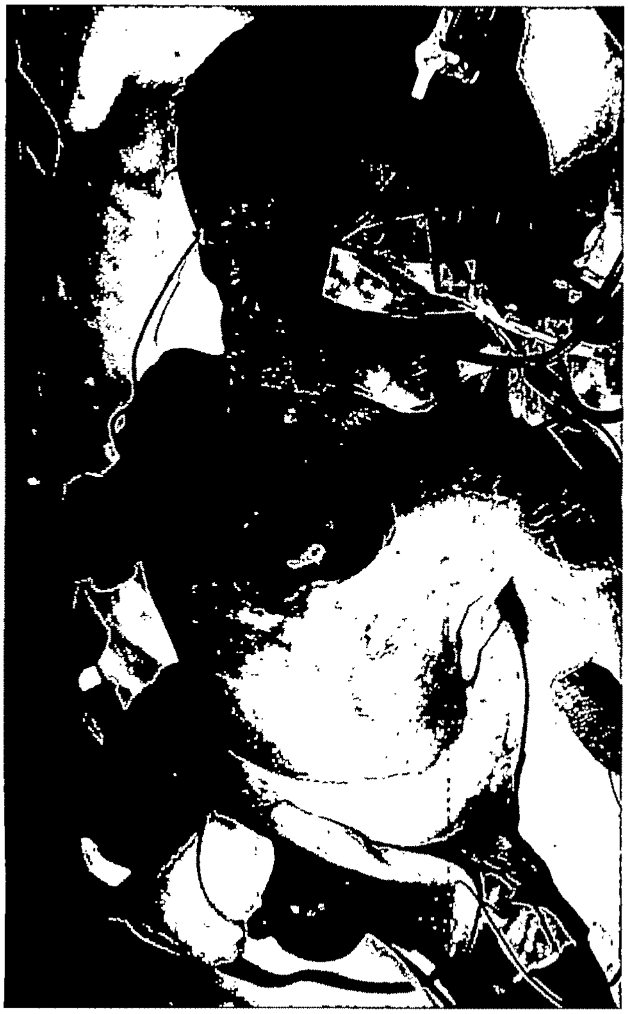

Fig 1. *Patient after resuscitation.*

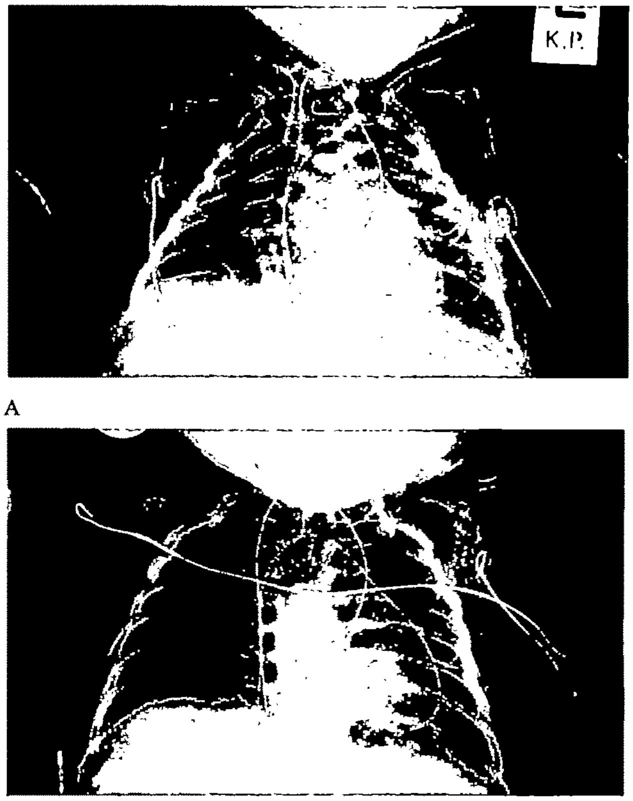

Fig 2. *Plain chest roentgenograms taken (A) immediately and (B) 9 days postoperatively.*

Comment

Survival after correction has been documented in the incomplete form of ectopia cordis [1–4] and also in the total thoracic form with no intracardiac defects [5] but not when the combination [6] exists. We reasoned that the best chance for survival would be immediate correction after birth. Sterility was maximized by using cesarean section in an adjacent operating room and covering the heart in sterile plastic immediately after birth. Sterile direct echocardiography was of use for preoperative planning. The intracardiac repair was performed in the usual manner under profound hypothermia and circulatory arrest. Expansion of the thoracic cavity proved to be technically feasible but depended on (1) widening the lateral and anteroposterior diameters by a rib slide maneuver as well as rib transection and detachment of the diaphragm from the inferior cartilaginous bar and (2) lengthening the cavity by lowering the diaphragm. The external orientation of the heart at right angles to the chest wall in our patient predisposed it to flow obstruction with minimal interference and the technical impossibility of in situ skin cover; thus placement back into the thoracic cavity was mandatory. Cardiopulmonary bypass was needed for this, and hence total internal cardiac repair was done at the same time. Although our patient did not survive, death was due to sepsis (with no focus being located in the thoracic cavity) rather than directly related to the repair itself.

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Successful Treatment of Acute Postoperative Pulmonary Hypertension With Nifedipine

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We report the successful use of nifedipine in the treatment of acute pulmonary hypertension in an infant after a cardiac operation. This patient had undergone total surgical correction of his truncus arteriosus malformation. He had signs of severe pulmonary artery hypertension unresponsive to hyperventilation, oxygenation, sedation, and a myriad of vasodilators. Nifedipine, 0.2 mg/kg every 4 hours, effectively treated his pulmonary artery hypertension and allowed for a smooth postoperative course and positive outcome.

(Ann Thorac Surg 1992;53:148–50)

Pulmonary hypertension is a serious cause of morbidity and mortality after surgical correction of congenital heart defects. Postoperative pulmonary hypertension is likely to develop in infants who have excessive pulmonary blood flow or pulmonary venous obstruction. Elevated pulmonary resistance may occur as a result of this pulmonary vascular overload. The high pulmonary resistance may impose an impedance load on the right ventricle, causing it to fail and, through its interdependence with the left ventricle, produce a low cardiac output state. The decreased systemic pressure lowers coronary perfusion and a vicious cycle of biventricular failure may ensue.

Oxygen, hyperventilation, alkalinization, and sedation are the mainstays of therapy for pulmonary hypertension in infants [1]. The lack of specific pulmonary vasodilators makes management of postoperative pulmonary hypertension difficult. If nonspecific vasodilators are used to lower pulmonary vascular pressure, systemic pressure may be simultaneously lowered, negatively affecting coronary perfusion to a hypertensive right ventricle. We report the successful use of the calcium channel blocker nifedipine to treat pulmonary hypertension without affecting systemic pressure.

A 4-month-old male infant with Type 1 truncus arteriosus underwent complete repair of his cardiac lesion. He had first been seen at the age of 3 months with a history of poor weight gain, tachypnea, and failure to thrive. Diagnosis was made by cardiac catheterization and he was placed on a regimen of digoxin and furosemide (Lasix; Hoechst-Roussel Pharmaceuticals, Somerville, NJ).

The patient was brought to the operating room and noninvasive monitors were placed. Anesthesia was induced with nitrous oxide, oxygen, and 0.5% halothane. Venous access was obtained and he was nasotracheally intubated using pancuronium bromide (Pavulon; Organon Inc, West Orange, NJ) for neuromuscular blockade. Invasive monitoring consisted of a right femoral arterial line and a double-lumen right internal jugular vein.

Maintenance anesthesia was provided with incremental boluses of fentanyl for a total of 65 μg/kg. The operation was performed with the patient on hypothermic cardiopulmonary bypass at periods of low flow and consisted of patch closure of the ventriculoseptal defect and truncus repair using a pulmonic homograft. At the completion of the operation, a left atrial and a pulmonary arterial line were placed by the surgeon. The patient was weaned off cardiopulmonary bypass on infusions of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of amrinone. In anticipation of pulmonary hypertension in the postoperative period, a dose of 10 μg/kg of fentanyl was given to the patient before transport to the intensive care unit.

In the immediate postoperative period, the pulmonary artery pressures ranged from 25% to 30% of the systemic pressure. During the night of operation, the patient was hyperventilated with 100% O_2 to maintain arterial CO_2 levels between 20 and 25 mm Hg. The patient continued to receive fentanyl, 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$. When the pulmonary artery pressures began to increase to approximately 50% of the systemic pressures, vasoactive drugs were used to manipulate the pulmonary artery pressures. The dosage of dopamine was lowered to 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and amrinone administration was continued at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Prostaglandins were given at a dose of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ through the pulmonary artery catheter, and the dose was increased to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Nitroglycerin was added at a dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Using these drugs, the systemic pressures remained stable and the pulmonary artery pressures decreased from 30% to 50% systemic. That evening, the patient had stable vital signs and a urine output of 2 to 3 $mL \cdot kg^{-1} \cdot h^{-1}$.

On the first postoperative day, the pulmonary artery pressures began to rise to 60% systemic. Elevations in

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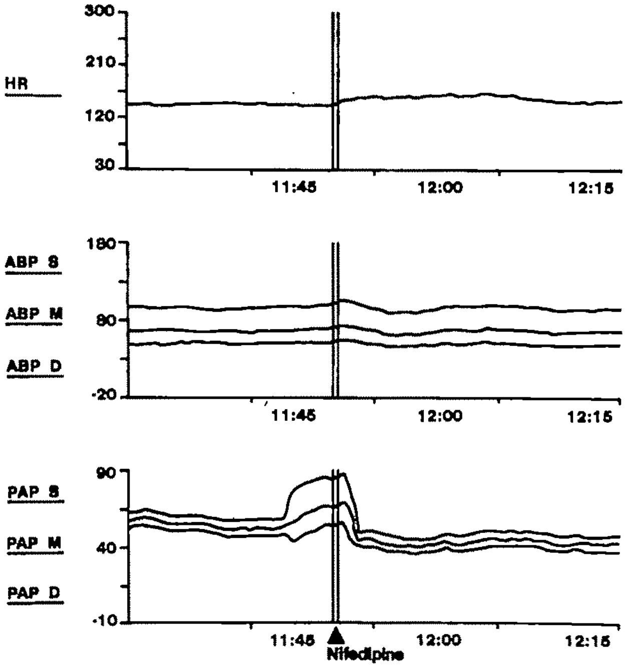

Fig 1. Simultaneous measurements of heart rate (HR), *arterial blood pressure* (ABP), *and pulmonary artery pressure* (PAP). (D = *diastolic;* M = *mean;* S = *systolic.*)

pulmonary artery pressure occurred in response to tracheal suctioning and spontaneously without a precipitating event. The fentanyl infusion was increased to 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the patient was further sedated with chloral hydrate and midazolam. Arterial carbon dioxide tension was kept in the range of 20 to 25 mm Hg. Arterial oxygen tension was kept greater than 200 mm Hg. Despite these pharmacologic manipulations, the patient's pulmonary artery pressures continued to rise and approached systemic pressures. Nifedipine, 0.2 mg/kg every 6 hours through the nasogastric tube, was given. The nifedipine was aspirated from a 10-mg capsule and diluted to a concentration of 1 mg/mL. The pulmonary artery pressures decreased by 50% with no impact on the systemic pressures, as shown in Figure 1. Throughout the evening, it later became necessary to increase the nifedipine dosing interval to every 4 hours to keep the pulmonary artery pressures less than 50% of the systemic pressure.

On the second postoperative day, the patient would intermittently have a pulmonary hypertensive crisis as evidenced by pulmonary artery pressures that became 60% systemic. The nifedipine dose was increased to 0.5 mg/kg every 4 hours, and the prostaglandin infusion was increased to 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Captopril was added at a dose of 2.5 mg three times a day through the nasogastric tube.

On the third postoperative day, the patient was weaned off dopamine and nitroglycerin. He continued to receive captopril, nifedipine, prostaglandin, and fentanyl infusion while we continued to monitor pulmonary and systemic pressure. Nitroglycerin ointment was substituted for nitroglycerin.

By the fifth postoperative day, the patient had no further episodes of pulmonary hypertension, he was further weaned from the drugs, and he was discharged home 2 weeks later, receiving 3 cm of nitroglycerin ointment every 3 hours.

Comment

Postoperative pulmonary hypertension with right ventricular failure is a particular problem in infants with increased pulmonary blood flow. Large systemic to pulmonary artery shunts occur in a variety of congenital heart defects including ventriculoseptal defects, transposition of the great vessels, atrioventricular canal, or truncus arteriosus. In other congenital defects such as mitral stenosis, cor triatriatum, and obstructed pulmonary veins, pulmonary hypertension is secondary to elevated pulmonary venous pressure. Pulmonary hypertension may complicate the postoperative course of patients with these defects despite adequate surgical repair [1].

A pulmonary hypertensive crisis is characterized by a rapid rise in pulmonary artery pressure. These episodes may occur randomly or may be triggered by specific factors such as agitation or tracheal suctioning. The elevated pulmonary artery pressures strain the right ventricle and, if left untreated, can evolve to ventricular failure and death. Often the pulmonary crisis can be effectively treated with oxygen, hyperventilation, and sedation. When these therapies do not suffice, vasoactive drugs such as tolazine hydrochloride (Priscoline; CIBA Pharmaceutical Co, Summit, NJ), prostaglandin, or prostacycline are added. An ideal drug for the treatment of acute pulmonary hypertension would act selectively on the pulmonary vasculature, increasing cardiac output with minimal effects on systemic pressures or the relationship between ventilation and pulmonary perfusion.

Nifedipine inhibits the transmembrane influx of extracellular calcium ions across myocardial and vascular smooth muscle cells, thereby promoting vasodilatation. As a pulmonary vasodilator, nifedipine may act locally within the lung vasculature or indirectly through the sympathetic nervous system, inhibiting hypoxic vasoconstriction [2]. Changes in vascular resistance induced by nifedipine are inversely related to the degree of arterial hypoxemia [3]. Nifedipine's efficacy as a selective pulmonary vasodilator is controversial. Prielipp and associates [4], studying the hemodynamic effects of a variety of vasodilators, found nifedipine to decrease systemic pressure more than pulmonary pressure. Other investigators refute this, showing that pulmonary artery pressures and resistance are preferentially reduced, particularly in adults and children with chronic obstructive lung disease and cor pulmonale [5–7]. Nifedipine has been proven beneficial in children, in whom chronic administration lowered pulmonary artery resistance, increased pulmonary performance, and produced subjective improvement [8]. Less is known about acute postoperative pulmonary vasculature effects of nifedipine in children. The only generalization that can be made regarding nifedipine as a pulmonary vasodilator is that patient response is variable.

In the case we report, nifedipine exhibited the properties of an ideal pulmonary vasodilator: it selectively lowered pulmonary artery pressure yet preserved systemic pressure and, indirectly, coronary perfusion, thus improving cardiac function. Nifedipine should be considered a therapeutic option in the treatment of acute postoperative pulmonary hypertension in children.

Addendum

Since the submission of this report, 6 additional patients with pulmonary hypertension after cardiac surgical repair were treated with nifedipine with good results. Nifedipine is currently the pulmonary vasodilator of choice at our institution.

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Primary Lung Cancer Producing α-Fetoprotein

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Reports of α-fetoprotein–producing lung tumors are rare. Only 24 such patients with these tumors have been previously studied. We report the case of a patient with a large cell carcinoma of the lung and a serum α-fetoprotein level of 9,300 ng/mL, with no evidence of hepatic or other systemic abnormalities. Serum levels of α-fetoprotein returned to normal postoperatively.

(Ann Thorac Surg 1992;53:151–2)

Since α-fetoprotein (AFP) was discovered in the serum of patients with hepatocellular carcinoma in 1965 by Tatarinov [1], this tumor marker has become a reliable diagnostic indicator of malignancies such as hepatocellular carcinoma [2] and yolk sac tumors [3]. Reports of primary lung cancers producing this tumor marker are quite rare, however. Herein, we present the case of a patient with an AFP-producing large cell carcinoma of the lung in which serum levels of the marker vanished after removal of the neoplasm.

A 49-year-old Japanese man was referred to Tokyo Medical College on October 30, 1987, complaining of a 1-month history of cough productive of bloody sputum. His general health was good and his physical examination was unremarkable. The chest roentgenogram revealed an abnormal opacity in the right upper lobe (Fig 1). Brushing specimens obtained at bronchoscopy were diagnostic of large cell carcinoma of the lung. The laboratory values obtained on admission, including a complete blood count, blood chemistries, and urinalysis, were within normal limits except for an elevated level of serum AFP. Serum AFP level was 9,300 ng/mL by radioimmunoassay. Other tumor markers including carcinoembryonic antigen, CA19-9, and CA125 were within the normal ranges. Although the serum AFP level was dramatically elevated, no abnormalities in liver function, as shown by a hepatic scintigram, abdominal computed tomographic scan, or ultrasonographic study, were evident. A right thoracotomy was performed on November 27, 1987. The tumor removed (6 × 5 × 5 cm) was located at the right segmentum apicale and was locally invasive to the chest wall supraclavicularly. A right upper lobe lobectomy with resection of the chest wall invaded by tumor along with a regional lymph node dissection was carried out. Microscopically, the tumor consisted of sheets of giant cells without glandular formation. The somewhat polymorphic and irregular nuclei were rich in chromatin, whereas the cytoplasm resembled the sinusoidal pattern seen in hepatocellular carcinomas. The pathological diagnosis was large cell carcinoma (Fig 2). The immunoenzyme labeling technique using the peroxidase-antiperoxidase method with anti-AFP immunoglobulin G antibody confirmed AFP secretion by these tumor cells. One week postoperatively, the serum AFP level was reduced to 207 ng/mL, and at 3 weeks, the level was within the normal range. The patient was disease-free with undetectable serum AFP levels 11 months after operation.

Comments

α-Fetoprotein is an oncofetal antigen that can now be quantitated by radioimmunoassay for confirming the diagnoses of hepatocellular carcinoma [2] and yolk sac tumors [3]. There is some evidence that certain gastric and pancreatic carcinomas [4], as well as primary lung tumors [5–7], may secrete AFP. One lung carcinoma producing AFP was reported in 1972 [8], but since there were metastases to the liver, the authors attributed AFP production to regenerating hepatocytes surrounding the metastatic lesions. In our survey of the literature, only 24 cases of AFP-producing lung carcinomas without metastasis to the liver have been reported, and Yoshimoto and co-workers have summarized these cases [5].

There are several hypothesis that can explain AFP production by primary lung tumors [8]. It is not surprising that lung parenchyma can retain a capability for AFP production, as this organ is derived from the primitive fetal gut, as are the liver, stomach, and pancreas [2]. Inspection of Table 1 reveals that 16 of 24 AFP-producing primary lung tumors were adenocarcinoma histologically. No squamous cell AFP-producing lung tumors have been reported. The histologic presentation is consistent with that seen in AFP-producing gastric and pancreatic adenocarcinomas, and consonant with a theory of common origin. The large cell adenocarcinoma in our patient shares the cytoplasmic feature of a hepatoidal or sinusoidal pattern as in hepatocellular carcinoma. This is in agreement with a theory of common origin as well as the "ectopic hepatoma" theory [6]. In patients with AFP-producing lung tumors, one must also consider the possibility of an extragonadal germ-cell cancer syndrome, especially if the tumor is undifferentiated or poorly differentiated [7].

Although all 24 cases of AFP were in Japanese patients

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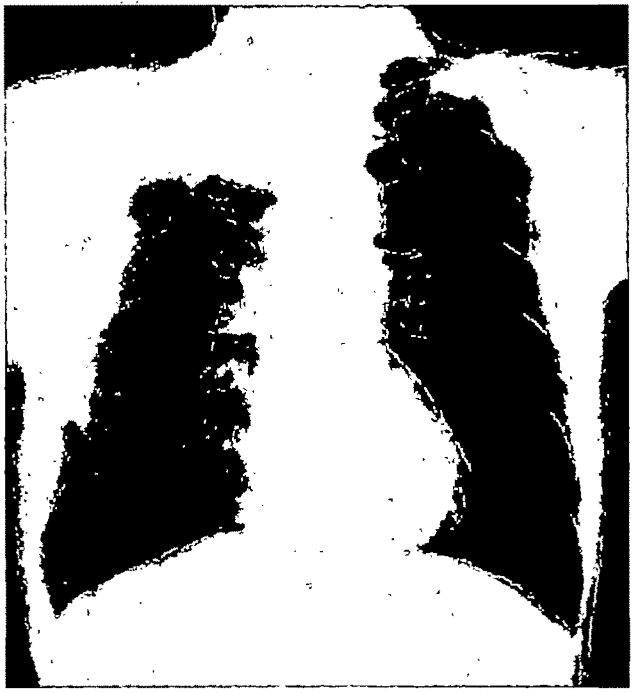

Fig 1. Chest roentgenogram on admission reveals an abnormal opacity in the right upper lobe.

Table 1. α-Fetoprotein–Producing Primary Lung Cancers Without Liver Metastasis

Variable	Value
Sex (M/F)	22:2
Age (y)	
Mean	65
Range	40–80
Histology	
Adenocarcinoma	
Well differentiated	2
Moderately differentiated	3
Poorly differentiated	11
Large cell carcinoma	6
Small cell carcinoma	1
Carcinoid tumor	1
Serum α-fetoprotein (ng/mL)	73,000–320,000

living in Japan, this may mean only that in Japan there have been many attempts to measure this marker. In no previous paper has data on the total number of cases measured been given; therefore, it is difficult to obtain an idea of how useful this marker will eventually become in the field of lung cancer. In 1987 AFP was serendipitously detected in a case of adenocarcinoma of the lung in which the radioimmunoassay was performed more out of curiosity than anything else. Subsequently it was decided to perform the procedure in all cases of adenocarcinoma, small cell, and large cell cancer of the lung for a given period of time. This decision was made because no reported case of squamous cell carcinoma of the lung producing AFP has been reported. The present case was the only positive case out of 350 cases measured subsequently. This would not be surprising given the rarity of these types of malignancies. More recent advances in the measurement of this oncofetal protein by affinity chromatographic studies with concanavalin A have led to the discovery of AFP isozymes [5]. Such advances may contribute to our understanding of the molecular biology of these interesting tumors.

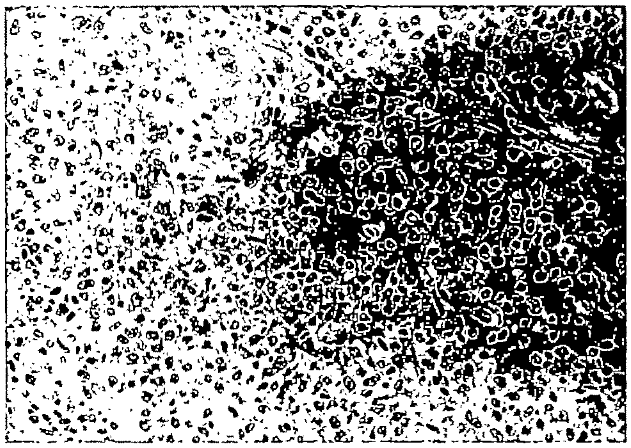

Fig 2. Large cell carcinoma from space-occupying mass shown in Figure 1 consisting of sheets of giant cells without glandular formation. (Hematoxylin and eosin, ×200 before 50% reduction.)

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Prognostic Significance of Massive Bronchogenic Tumor Embolus

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Massive arterial bronchogenic tumor embolus is rare, and most commonly occurs intraoperatively during pulmonary resection. Arterial obstruction from the tumor embolus carries substantial morbidity and mortality. For those patients who survive embolectomy, prognosis is most closely correlated with the TNM staging of the primary lung tumor ignoring the tumor embolus.

(Ann Thorac Surg 1992;53:153–5)

Massive arterial bronchogenic tumor embolus is rare. For those patients who survive embolectomy, how this event affects their lung cancer staging and prognosis has not been addressed. A survivor of massive bronchogenic tumor embolus is reported, and the prognosis discussed.

The patient is a 60-year-old nonsmoker who had a persistent, nonproductive cough. A chest roentgenogram showed a new left hilar mass. A chest roentgenogram 5 years earlier had been normal. The patient's past medical history was significant for hypertension and a thyroid Hurthle cell adenoma treated by right thyroid lobectomy. On physical examination, there was no peripheral adenopathy. Breath sounds were clear and equal bilaterally, there were no cardiac murmurs, and the pulse was regular. The patient's forced expiratory volume in 1 second was 1.67 L (90.5% predicted). Contrast-enhanced computed tomography of the chest and abdomen showed aorticopulmonary lymphadenopathy and a large left mid-lung field tumor which abutted the pericardium (Fig 1). Flexible fiberoptic bronchoscopy revealed thickening of the endobronchial spur between the left upper and lower lobes. Endobronchial biopsy revealed large cell lung carcinoma.

A left thoracotomy was performed. On exploration, there was a 10 × 8 × 6-cm mid-lung field tumor centered in the lingula which crossed the fissure to involve the lower lobe. Medially the tumor was adherent to the pericardium and phrenic nerve. The enlarged aorticopulmonary window and subcarinal lymph nodes were completely excised and were negative for tumor by frozen section. The pericardium was opened and an intrapericardial pneumonectomy performed excising en bloc a portion of involved pericardium and phrenic nerve. An attempt was made to divide the pulmonary veins as the first step. However, after the inferior vein was ligated and divided, the superior vein was noted to contain a rubbery mass which extended into the left atrium consistent with intravascular extension of tumor. With the large central lung tumor, it was believed that there was insufficient exposure to control the left atrium and to divide the superior pulmonary vein without further mobilization. The left main pulmonary artery was therefore ligated and divided. On reinspection, the intravascular mass in the superior vein was no longer present. The patient remained clinically unchanged, the pneumonectomy was completed, and the patient was taken to the intensive care unit.

In the immediate postoperative period, the patient was awake, neurologically intact, and hemodynamically stable with a regular pulse. The abdominal examination was benign, the peripheral pulses were full symmetrically, and the urine output was maintained. Twelve hours postoperatively the patient complained of left leg pain. A duplex scan showed a distal aortic saddle embolus obstructing the left iliac artery. The patient underwent aortoiliac embolectomy through a left retroperitoneal approach, restoring pulses to the left leg. Pathologic examination of the embolus revealed thrombus and large cell tumor similar to the lung tumor (Fig 2). Final pathology on the resected lung showed a 10 × 7.8 × 6-cm large cell lung tumor with negative surgical margins, and all sampled lymph nodes were negative for tumor. The patient is currently alive with no evidence of disease 20 months postoperatively.

Comment

Massive tumor embolus, especially during pulmonary resection, carries substantial morbidity and mortality;

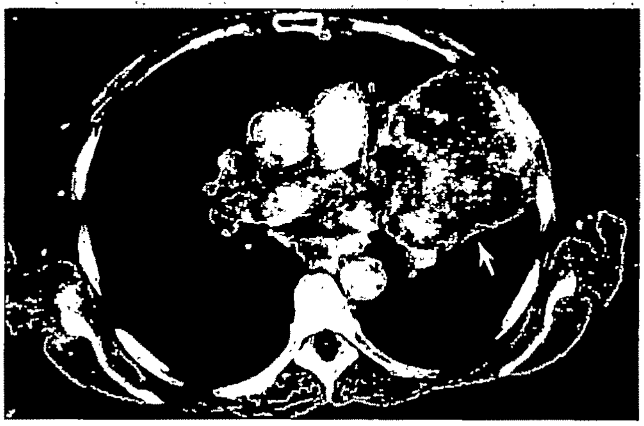

Fig 1. Computed tomographic scan showing large, central lung tumor abutting the pericardium (tumor indicated by arrow).

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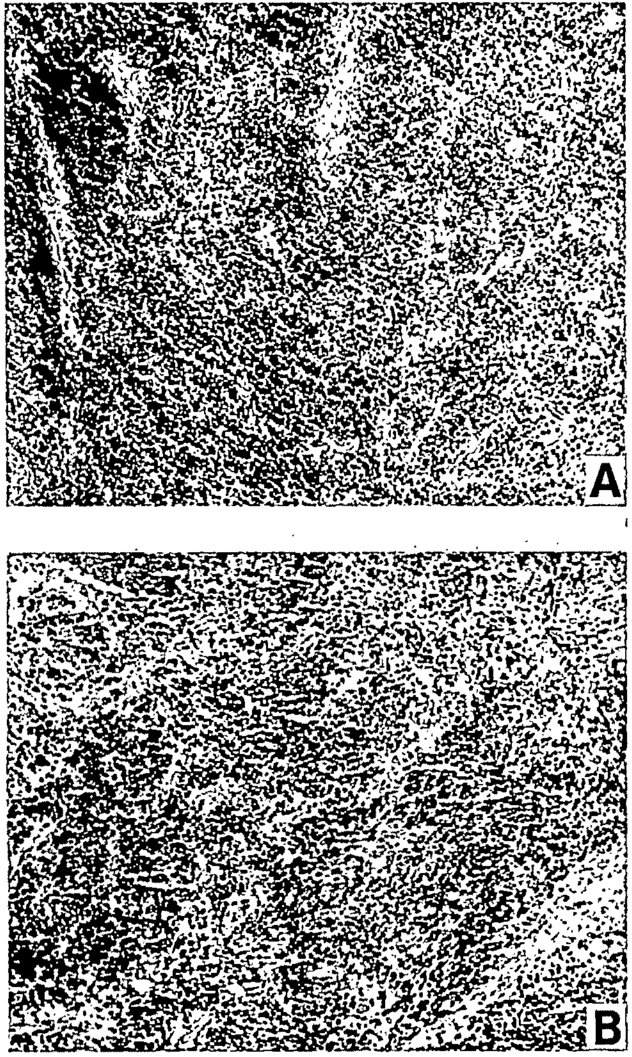

Fig 2. Photomicrographs of massive tumor embolus showing large cell tumor (A) with necrosis, and the primary large cell lung tumor (B). (×160 before 28% reduction.)

nonetheless, it is not uniformly fatal, and multiple cases of successful embolectomy, including our patient, have been reported [1–5]. For those patients with non–small cell lung carcinoma who survive embolectomy, how this event affects lung cancer staging and prognosis has not been addressed.

Table 1 summarizes the reported cases of patients with massive non–small cell bronchogenic tumor embolus who survived embolectomy and for whom both survival and TNM staging information were available. Prioleau and Katzenstein [5] reported 4 patients with survival ranging from 3 to 7 months. Three patients had known metastasis on presentation. The fourth patient, who underwent a right pneumonectomy for a presumed T2 N1 M0 adenocarcinoma, had an incomplete resection (residual tumor at the pulmonary venous margin) and probably had unrecognized metastatic disease at the time of her operation accounting for the early (4 months) postoperative diagnosis of brain metastasis. Firor and Pearson [6] reported a patient who underwent right pneumonectomy with early (2 months) postoperative brain and subcutaneous metastasis. Again, the early development of clinically apparent postoperative metastatic disease suggests that the patient had unrecognized metastatic disease at the time of initial presentation. Blum [7] reported a patient with a squamous tumor obstructing the right main bronchus, with metastasis to the right ninth and tenth ribs. The patient died without pulmonary resection 2 months later. The median survival for these 7 patients was 4.5 months (range, 2 to 7 months). The expected median survival for non–small cell lung cancer patients with metastatic disease is 6 months [8]. Our patient underwent a left pneumonectomy for a T3 N0 M0 large cell tumor. The median expected survival for such a patient is 26 months [8]. This patient is currently alive and without evidence of recurrent disease 20 months postoperatively.

Zetter [9] argues that five steps must be completed for a tumor cell to successfully metastasize. These steps include the development of a primary tumor, entry of the tumor

Table 1. TNM Staging and Survival in Patients With Massive Bronchogenic Tumor Embolus

Author	Age (y)	Sex	Histology	TNM Classification	Arterial Embolic Site	Lung Resection	Survival (mo)
Prioleau and Katzenstein [5]	56	F	Adenocarcinoma	T2 N1 M0 (?M1)	Distal aorta	Right pneumonectomy	5
	53	M	Squamous cell	T2 N1 M1	Left axillary	Right lower lobe	5
	67	F	Squamous cell	T1 N2 M1	Bilateral femoral	None	7
	69	M	Adenocarcinoma	T2 N1 M1	Distal aorta	Right upper lobe	3
Firor and Pearson [6]	43	M	Squamous cell	T2 N0 M0 (?M1)	Distal aorta	Right pneumonectomy	5
Blum [7]	60	M	Squamous cell	T2 (?T3) N1 M1	Left common femoral	None	2
Heitmiller	60	F	Large cell	T3 N0 M0	Distal aorta	Left pneumonectomy	Alive, with no evidence of disease at 20 months

into the vascular or lymphatic system, endothelial adherence at a secondary site, local invasion, and finally proliferation at this secondary site. Patients with massive tumor emboli complete the first two steps; however, these emboli do not adhere to the arterial endothelium in a site-specific fashion, but rather embolize and become entrapped at their respective lodgement sites. Further, embolectomy should prevent local invasion and tumor proliferation. Others have shown experimentally that "passive" lodgement of tumor cells does not invariably lead to secondary tumors [10, 11].

Metastatic disease, separate and unrelated to the massive tumor embolus, is common in patients with massive bronchogenic tumor emboli most likely as a consequence of the direct vascular invasion by tumor with micrometastasis. For patients with massive tumor emboli, the embolic event carries substantial morbidity and mortality. For those patients who survive embolectomy, prognosis is most closely related to the TNM staging of the primary lung tumor ignoring the tumor embolus.

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Angiographic Demonstration of No-Flow Anatomical Patency of Internal Thoracic–Coronary Artery Bypass Grafts

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To clarify the no-flow situation of the stringlike internal thoracic artery graft, we angiographically examined such grafts by temporarily occluding the recipient coronary artery with a percutaneous transluminal coronary angioplasty balloon and were able to reveal anatomical patency of the internal thoracic artery graft in 2 patients 1 year and 3 years after the operations. Thus, there is a possibility that internal thoracic artery grafts may continuously maintain anatomical patency even under no-flow situations just like nonfunctioning collateral vessels and may function properly later as a graft when the native coronary flow decreases. Also, this angiographic technique can be a new method for detecting anatomical patency of no-flow and functionally closed internal thoracic artery grafts.

(Ann Thorac Surg 1992;53:156–9)

It is known that some internal thoracic artery (ITA) grafts become very thin and exhibit a so-called string sign with no demonstrable flow of the contrast material into the recipient coronary artery. However, the question how such an ITA graft will change with time or whether the graft can maintain its anatomical patency continuously for a long time has not yet been answered. We angiographically demonstrated anatomical patency of the ITA graft in spite of its string sign with no-flow situation in 2 patients 1 and 3 years after the operations by virtue of temporary occlusion of native coronary blood flow using the balloon of a percutaneous transluminal coronary angioplasty catheter.

Two male patients, 64 and 50 years old, underwent coronary artery bypass grafting with an ITA in situ anastomosed to the left anterior descending coronary artery (LAD). Preoperatively, they had angina pectoris and their coronary arteriography was judged to show 95% and 75% stenosis in the LAD. Single left ITA grafting was performed to the LAD in 1 patient and quadruple grafting including a right ITA to the LAD was carried out in the other patient. The internal diameter of the ITA was approximately 2.0 mm in each patient. After the operation, the patients have not been aware of any angina pectoris, and myocardial ischemia in the LAD region was not observed by exercise electrocardiography or 201-thalium scintigraphic examinations.

Three years and 1 year after the operations, coronary arteriography was repeated to confirm patency of each graft, although the patients were both asymptomatic. In both patients after the operation, stenosis of the LAD was apparently improved (less than 25% in each case) with substantial regression of atheromatous plaque, and ITA grafts showed thinning longitudinally, a string sign, as shown in Figures 1a and 2a. Flow of the contrast material from the ITA to the LAD was not demonstrable in either patient, and the grafts were judged at least functionally closed. At this moment, we explained the situation to the patients and obtained full consent for further angiographic examinations with the use of a percutaneous transluminal coronary angioplasty balloon. Native flow in the LAD was temporarily interrupted by occluding the LAD with a percutaneous transluminal coronary angioplasty balloon, then ITA angiography was repeated. As shown in Figures 1b and 2b, the flow from the stringlike ITA into the LAD was now clearly observable. When native flow was intercepted, the bloodstream from ITA to LAD increased and the anatomical patency of ITA grafts could be demonstrated on angiographic images.

Comment

Various causes of ITA graft longitudinal thinning have been put forth as follows: (1) competitive flow phenomenon in which ITA flow decreases because of flow competition with unimpeded native coronary flow [1–3]; (2) steal phenomenon in which, if a large branch of the ITA remains undivided, the flow after bifurcation of this branch decreases and the ITA becomes thinned [4]; (3) ITA spasm [5]; (4) circumferential inflammation of the ITA in postpericardiotomy syndrome [5]; and (5) burns of the ITA caused by electrocautery [5]. Among them, we consider the thinning of ITA graft to be mainly caused by flow competition when a stenotic lesion of the recipient vessel is mild or regressed, and also when myocardial ischemia

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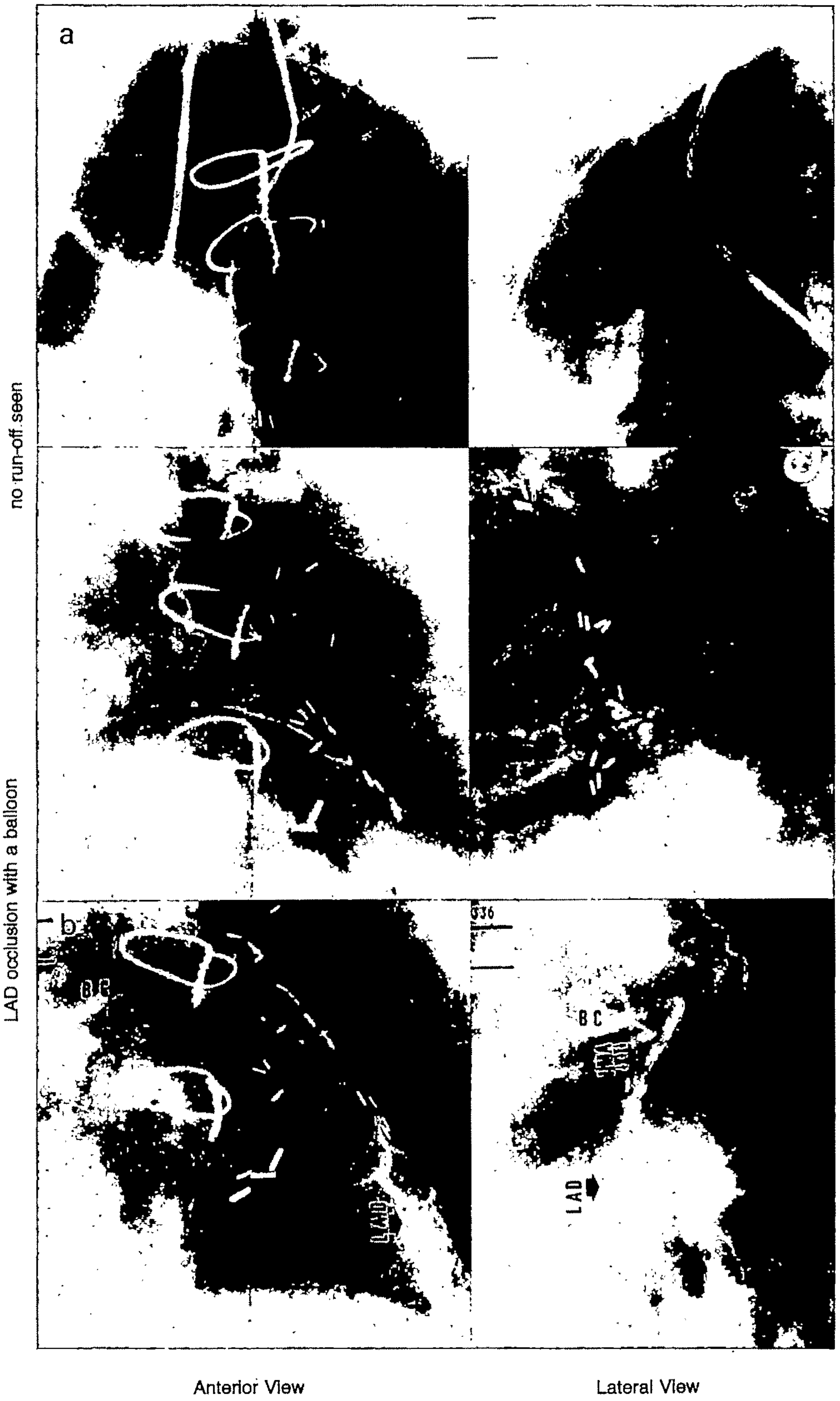

Fig 1. (Patient 1.) (a) Postoperative (3 years) left internal thoracic arteriography showed a string sign of the graft with no inflow of contrast medium into the left anterior descending artery (no-flow situation). (b) With temporary occlusion of the proximal left anterior descending artery (LAD) by a percutaneous transluminal coronary angioplasty balloon (BC), left internal thoracic arteriography now demonstrated inflow of the contrast material into the coronary artery, revealing anatomical patency of the no-flow internal thoracic artery graft (IMA).

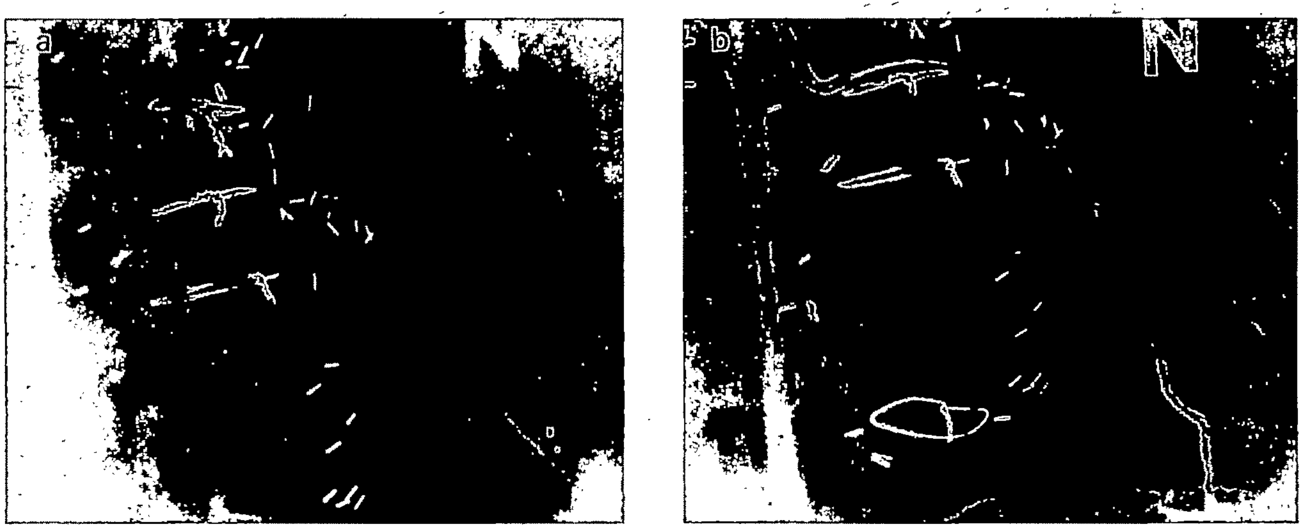

Fig 2. (Patient 2.) (a) A stringlike left internal thoracic artery graft with no-flow into the left anterior descending artery. (b) Repeated left internal thoracic arteriography now showing anatomical patency of the graft, demonstrated by temporary occlusion of the recipient left anterior descending artery with a percutaneous transluminal coronary angioplasty balloon.

in the relevant region is absent. Dincer and Barner [1] reported a case wherein the ITA graft became patent again in the angiographic examination 4 years after the operation when the LAD lesion had progressed from 80% to 95%, although it was not angiographically patent 1 year after the operation. Aris and co-workers [2] and we [6] also reported similar cases in that ITA grafts were judged nonpatent in the early postoperative angiograms, but late after the operation, the ITA graft became patent in accordance with the progressing stenosis of the bypassed coronary artery.

In our 2 patients, it is thought that blood flow of the ITA graft was markedly reduced due to unimpeded native LAD flow (flow competition between ITA and LAD) resulting in the so-called string phenomenon. Because inflow of contrast medium from the ITA to the LAD was not able to be proved by usual angiography, these ITA grafts were considered to be closed. However, we could demonstrate the anatomical patency of the no-flow ITA graft by angiography when we temporarily occluded native coronary artery flow with a percutaneous transluminal coronary angioplasty balloon. Therefore, the ITA graft involved was apparently in the situation where antegrade graft flow was hardly present; namely, the graft was functionally closed (no-flow situation) but anatomically patent just like a regressed collateral vessel. We believe that this angiographic technique can be a new method for detecting anatomical patency of the functionally closed ITA graft, although it should be carried out with caution.

Our present cases showed regression of LAD lesions postoperatively. Regression of coronary artery stenotic lesions has been demonstrated by repeated angiography in 15 of 317 patients (4.7%) in one series [7] and in 7 of 227 patients (3.1%) in another series [8]. We have seen ITA grafts in no-flow situations in 5 of the 142 (3.5%) consecutive grafts evaluated by postoperative angiography. This incidence was quite similar to that reported for regression of coronary lesions [7, 8]. Because we have not performed angiography with temporary closure of the recipient coronary artery in all patients, we do not know the true incidence of no-flow but anatomically patent ITA grafts. However, two of the three grafts thus tested maintained anatomical patency. Therefore, we believe that the incidence of no-flow but anatomically patent ITA grafts is not low.

No signs of ischemia in the relevant region were observed either in clinical symptoms or by myocardial scintigraphic examinations. Thus, the blood flow through the native coronary artery that showed regression of a stenotic lesion was considered sufficient to make the ITA graft unnecessary and make the ITA graft undergo the string phenomenon. It should be stressed from our observation that the no-flow ITA graft maintained its anatomical patency for a period of 3 years in patient 1 and 1 year in patient 2. As previously described [1, 2, 6] it is possible that stringlike and no-flow ITA grafts can enlarge and become functionally patent again when stenosis of the bypassed coronary artery is advanced in certain patients in whom technical problems of anastomosis including graft injury during dissection [5] can be ruled out. The ITA graft in situ is thought to have functioned as an operatively prepared collateral vessel.

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INVITED COMMENTARY

This report further corroborates previous observations suggesting the physiologic potential of the internal thoracic artery to dilate and contract depending on demand. If corroborated, this should reduce the surgeon's concern about using the internal thoracic artery grafts in competitive flow situations. Further, it should encourage angiographers to investigate the potential of this test for evaluating patients with a string sign before reoperation. It is conceivable that a substantial proportion of the patients with a string sign do not need to have the conduit replaced at the time of reoperation or may not need the reoperation at all. Such observations could have major implications on the angiographic indications for and the planning and the execution of a reoperation. It is hoped that the angiographers will further evaluate the usefulness of this technique.

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New Needle for Catheter Introduction in Left Atrium

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We describe a new needle for left atrial catheter introduction. It allows catheter introduction through the right superior pulmonary vein or through the interatrial septum. Used in 32 patients (adults and children), the device proved to be highly efficient, simple, and safe.

(Ann Thorac Surg 1992;53:160–1)

Catheter placement in the left atrium is a common procedure in cardiac surgery. It permits adequate monitoring of left atrial pressure and estimation of left ventricular function, mainly during weaning from cardiopulmonary bypass. Occasionally the catheter is essential in the first hours postoperatively [1, 2]. The techniques presently used for the placement of the catheter are time consuming and frequently cause angulation or kinking.

Material and Methods

A new needle has been designed to facilitate left atrial catheter introduction. This needle has a groove in the lateral distal portion (Fig 1A), which allows the introduction of the catheter into its lumen (Fig 1B). The proximal portion of the needle has a holder of a variable length. The needle can be introduced through the right superior pulmonary vein (Fig 2) or even directly through the interatrial septum (Fig 3) if a catheter has been previously introduced through a central or peripheral vein [3].

The needle with the catheter in its groove (Fig 4A) perforates the atrial septum or the pulmonary vein and is pushed a few millimeters. Once in the left atrium, the catheter is held firmly and the needle is only moved forward just enough to let free the tip of the catheter (Fig

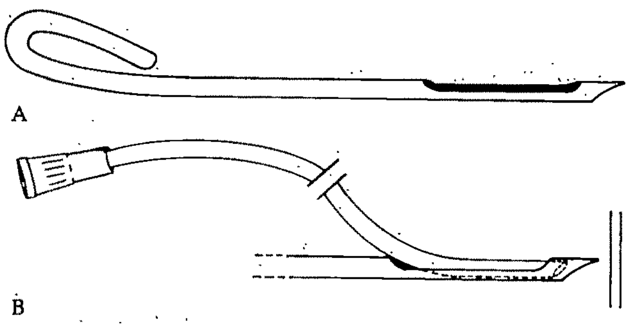

Fig 1. Design of the needle without (A) and with (B) catheter.

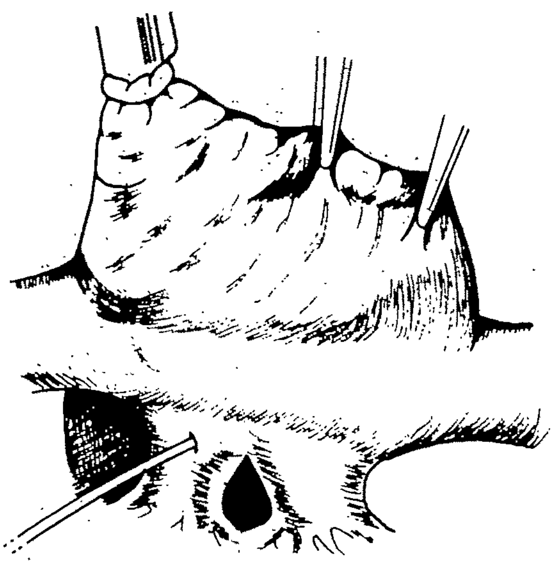

Fig 2. Place where the catheter is usually introduced (right superior pulmonary vein).

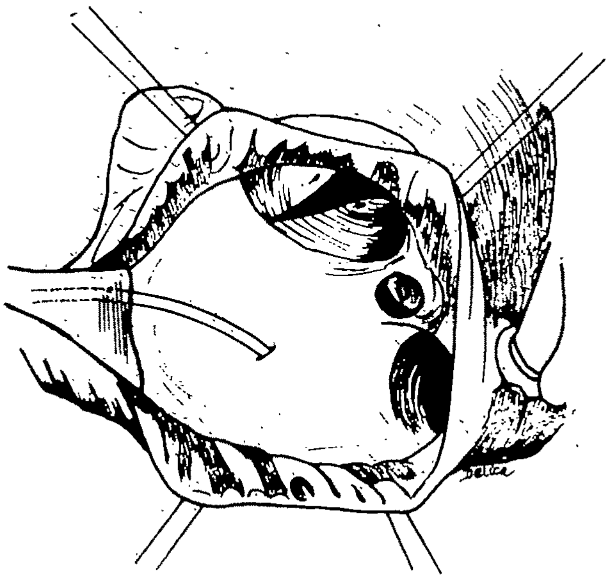

Fig 3. Place in interatrial septum where the catheter is introduced.

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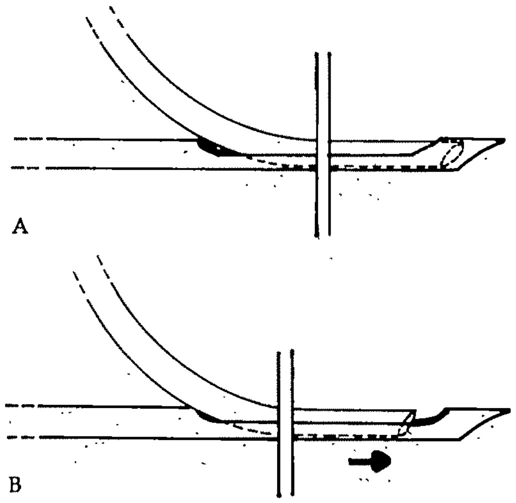

Fig 4. Needle with catheter is introduced through the wall (A), and with the catheter held firmly, the needle is moved forward a few millimeters (B).

4B). After this, the needle is rotated 180 degrees and the catheter now comes off the groove, remaining side by side with the needle (Fig 5A). The catheter is kept in the cavity while the needle is removed (Fig 5B).

Thirty-two patients (adults and children) were submitted to this new technique, and no complications were noticed.

Comment

The needle described is effective and simple. It produces a minimal orifice in the atrial septum or pulmonary vein wall, eliminating the necessity for sutures when the catheter is removed, which is very helpful in cardiac operations.

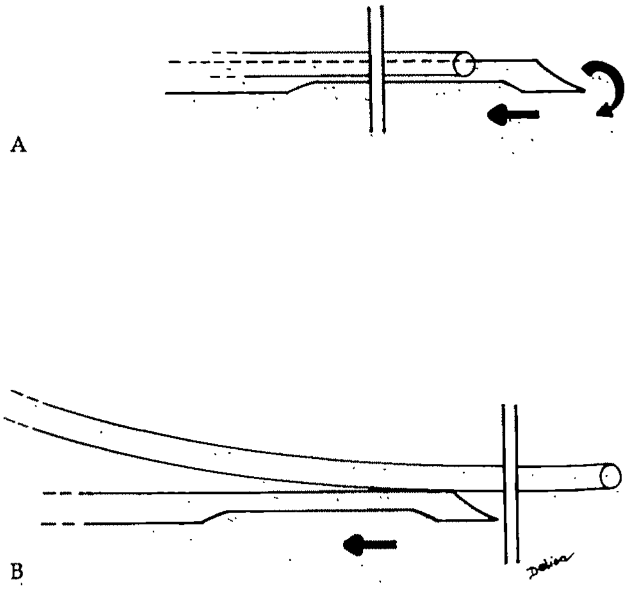

Fig 5. The needle is rotated 180 degrees (A) and removed from the cavity (B).

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Sheathless Insertion of the Percutaneous Intraaortic Balloon Pump: An Alternate Method

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A technique is described that allows insertion of a standard percutaneous intraaortic balloon without use of the larger 12F sheath. Standard 9.5-cm. Percor balloons were inserted in a series of patients without using the provided sheath. Elimination of the sheath reduced the potential vascular complications related to the extra bulk placed in the femoral artery by the sheath. No serious complications were noted in more than 25 patients.

(*Ann Thorac Surg 1992;53:162*)

Clinical application of the intraaortic balloon pump was introduced by Kantrowitz and associates [1] in 1968. Intraaortic balloon pumping is widely accepted as a first-line mechanical modality for the treatment of left ventricular power failure. The clinical application of balloon pumping was limited by the fact that it required a surgical team to implant. The introduction of the percutaneous balloon pump in 1978 [2] permitted wider application of this device. The percutaneous balloon is usually inserted by a modified Seldinger technique [3] through a 12F sheath. In a subgroup of patients with small or diseased arteries, the intraaortic balloon pump combined with a 12F sheath can obstruct the femoral artery with resultant vascular complications [4]. This report describes a technique for sheathless insertion of the percutaneous intraaortic balloon pump.

Material and Methods

The Percor balloon is a 40-mL polyurethane balloon folded in such a way as to provide easy introduction through a sheath or over a guidewire. All balloons were off-the-shelf items and were not modified in any manner. To reduce the potential vascular complication related to the 12F sheath, a series of Percor balloons was purposely inserted in a sheathless fashion as follows: All insertions were through the common femoral artery. The groin was prepared, draped, and anesthetized in the usual fashion. The common femoral artery was punctured, and a guidewire was passed through the needle and directed into the thoracic aorta. The skin and subcutaneous tissue were dilated with the two graduated dilators down to the artery. The central wire stylet of the intraaortic balloon was removed, and the balloon was passed over the guidewire through the subcutaneous tissue into the vessel. Care was taken to gently rotate the tip of the balloon through the subcutaneous tissues into the common femoral artery so that it did not twist or buckle. The guidewire was held taut as it exited from the central port of the balloon. With adequate placement of the balloon through the femoral artery into the descending thoracic aorta, the guidewire was removed and the central lumen connected for pressure monitoring. Balloon pumping was then initiated.

Comment

Since its first clinical application by Kantrowitz and coworkers [1] in 1966, the intraaortic balloon pump has been the most commonly used mechanical therapy for ventricular power failure. The insertion techniques have evolved from the surgical cut-down [5] to percutaneous insertion with a sheath [2] to the described technique of sheathless insertion. No serious complications have been noted in more than 25 patients when sheathless insertion was used. In addition, no serious bleeding or retroperitoneal hematoma has been experienced. The absence of peripheral vascular complications distal to the balloon have led us to adopt this as our primary technique for balloon pump insertions. We use a pursestring suture around the puncture site to seal it on the balloon shaft, which limits any bleeding from the arteriotomy through the skin puncture site. Bleeding was experienced in 1 patient and was easily controlled by placement of a second pursestring suture. We suggest other physicians consider using the sheathless insertion technique as an alternative to the method of inserting the balloon through the sheath.

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Methylene Blue Guidance for Simplified Resection of a Lung Lesion

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A 60-year-old patient returned 1 year after right pneumonectomy with a new primary squamous cell carcinoma of the left lower lobe. Using fluoroscopic guidance, the lesion and the shortest track to the surface were marked by methylene blue preoperatively. The lesion was easily excised by wedge resection without the need for manipulation or deflation of the lung.

(Ann Thorac Surg 1992;53:163–4)

Approximately 3% of all patients undergoing lung resection will require a second resection for a metachronous lesion. The operative mortality has been reported by Mousset and associates [1] to be as high as 14.7% for the second procedure as compared with 3.5% for the first procedure. The morbidity and mortality are probably even higher for patients who have undergone previous pneumonectomy. The key to decreasing the morbidity and mortality during the second thoracic procedure lies in minimizing the trauma to the remaining lung tissue and in limiting the extent of resection. We describe a technique to localize a lung lesion and facilitate resection without deflation or contusion of the residual lung parenchyma.

Material and Methods

A 60-year-old man underwent right pneumonectomy for a stage I squamous cell carcinoma of the right upper lobe: T2 N0 M0. Seven months after his pneumonectomy, he was noted to have a new 5-mm coin lesion in the left lower lobe on computed tomographic scan. Six weeks later a repeat computed tomographic scan showed no change in size. Fourteen months after his resection, however, a repeat chest roentgenogram and computed tomographic scan revealed a definite enlargement in this left lower lobe lesion. He was referred for evaluation. A metastatic evaluation was negative. Bronchoscopy revealed no obvious lesion, and no abnormality was seen in the right bronchial stump. Fine-needle aspiration of the lesion was complicated by pneumothorax and severe respiratory distress, requiring chest tube thoracostomy. Pathologic examination of the fine needle aspirate was consistent with squamous cell carcinoma of the lung. Pulmonary function tests revealed moderate to severe obstructive disease. The patient was admitted for possible wedge resection.

On the morning of operation, the patient was sedated using 3 mg of intravenous midazolam (Versed; Roche laboratories, Nutley, NJ). A 28F left chest tube was placed sterilely using local anesthesia. The chest tube was used to prevent movement of the lesion during needle localization if a pneumothorax were to occur. The patient was then placed on the fluoroscopy table in the right lateral decubitus position. Using sterile technique a 20-gauge localizing needle was placed in the left midaxillary line, perpendicular to the skin. Using magnification fluoroscopy, the needle was guided into the lesion, and the needle position was verified in orthogonal planes. Once location was confirmed, 0.1 mL of methylene blue was injected into the lesion, and the injection was continued as the needle was withdrawn. Thus the lesion, the needle tract, and the skin exit site were marked with 0.4 mL of methylene blue.

The patient was then taken to the operating suite for thoracotomy and wedge resection. The methylene blue clearly marked the adjacent intercostal space and the area of the lower lobe that was to be resected (Fig 1). Wedge resection was then completed using linear cutting staplers, without the need for manipulation or deflation of the lung. The patient's postoperative course was uncomplicated, and he was discharged after 5 days.

Comment

The risks in performing a second lung resection are dependent on the extent of the proposed resection as well as the underlying lung disease [1, 2]. This is especially true in patients with poor pulmonary function and those who have previously undergone pneumonectomy. To avoid intraoperative contusion and deflation of the lung parenchyma we describe a technique of preoperatively marking the skin, and the shortest track to the lesion, with methylene blue. The advantages of this technique are twofold. First, this allows wedge resection, using a staple or electrocautery technique, without the need for manipulation of the lung. Contusion of the lung is thus avoided. Second, to delineate the lesion, deflation of the lung is not necessary, thus maximum pulmonary function is maintained during the procedure. This is extremely useful in patients whose condition has been compromised by a previous pneumonectomy.

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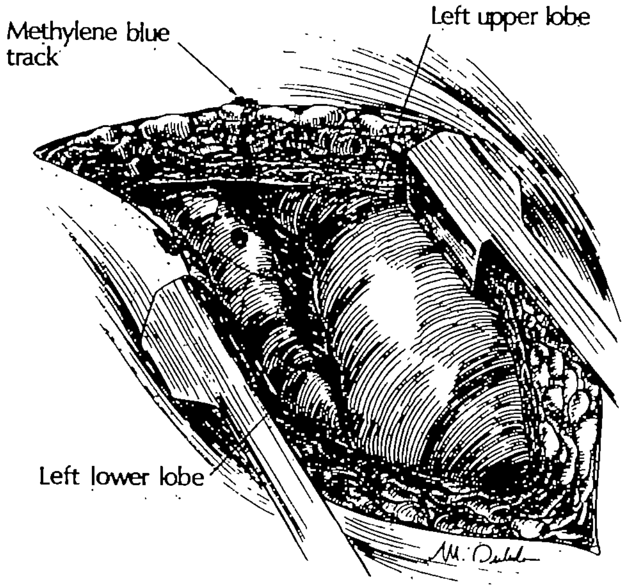

Fig 1. Methylene blue injection marks the shortest path to the lesion.

Localizing the lesion requires fluoroscopy and the use of methylene blue dye. The amount of dye used should be kept to a minimum, usually less than 0.5 mL, to prevent diffuse staining and detraction from the technique.

Marking a lesion with methylene blue before resection is not a new concept. It has been adopted widely in the localization and excision of breast lesions for many years [3]. Recently it has also been described in localizing individual mammary ducts that are to be excised owing to bloody nipple discharge [4]. Methylene blue has also been advocated in precisely marking abnormal bone scan findings suspicious for malignant disease [5]. This technique is not recommended for most lung resections, but when wedge resection is indicated, it can be useful in high-risk patients in whom it is desirable to avoid manipulation and deflation of the lung. Preoperative color identification may also prove useful when a lung lesion is removed at thoracoscopy. The potential value of this application will likely be determined shortly.

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Improved Technique for Hilar Vascular Stapling

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The use of stapling instruments is common in thoracic surgery, but there is a continued reluctance to use them on hilar vascular structures. We have developed a technique that satisfies the major objections to stapler use on hilar vascular structures.

(Ann Thorac Surg 1992;53:165–6)

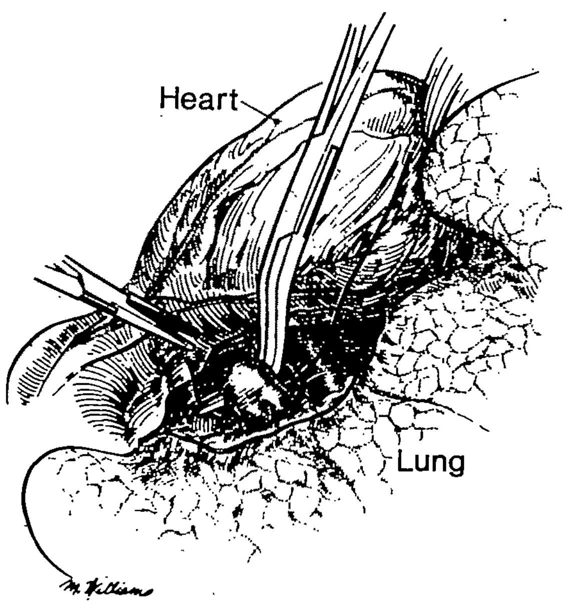

Fig 1. The Semm clamp carries a silk ligature behind the pulmonary artery or vein.

Over the last decade thoracic surgeons have become proficient in the use of surgical stapling instruments [1–3]. There is continued reluctance to use stapling devices on hilar vascular structures, however. This reluctance arises from two principal concerns.

The first concern is the act of faith involved in cutting on a closed stapling device, particularly when it has been applied to the pulmonary artery, and trusting when opening the device that staples have, indeed, been fired. Every surgeon has anecdotal experience of misfired staples leading to prolonged bleeding from the pulmonary artery and requiring sutures.

The second objection arises from the need to remove and then replace the stapler under the pulmonary artery or pulmonary vein after a previous staple line has been placed. Fear of the so-called "postage stamp effect," which may cause a vascular tear, has prevented many surgeons from attempting a second placement of the stapler. We have developed a simple technique for vascular stapling that we believe addresses these major objections to its use.

Technique

Step one is to dissect adequately the main pulmonary artery or main pulmonary veins from the surrounding tissues for approximately 1.5 cm (Fig 1). With the pulmonary artery a 1-0 silk suture is then placed around the major vessel using a Semm suture carrier instrument. Great care is taken to avoid opening or closing the instrument while it is securely behind the pulmonary artery to prevent inclusion of the vascular wall in the clamp. After a ligature is placed in a clamp, the clamp is passed behind the vascular structure and the suture pulled from its tips (see Fig 1).

Next, the suture is pulled away from the cardiac side of the vascular structure, gently snugging up and lengthening the segment of vascular wall exposed. A reloadable, disposable stapler (Ethicon, Somerville, NJ) is then placed behind the structure in position. After the pin is secured, the vascular stapler is closed, appropriate precautions are taken to be sure the appropriate staple length has been attained, and then the stapler is fired (Fig 2).

After this, three maneuvers are required to open the stapler. First, the pin is retracted; second, the lever is opened from behind and the safety placed; and last, the jaws are opened. Next, to place the second staple line in order to cut on the anvil and avoid disturbing the cardiac

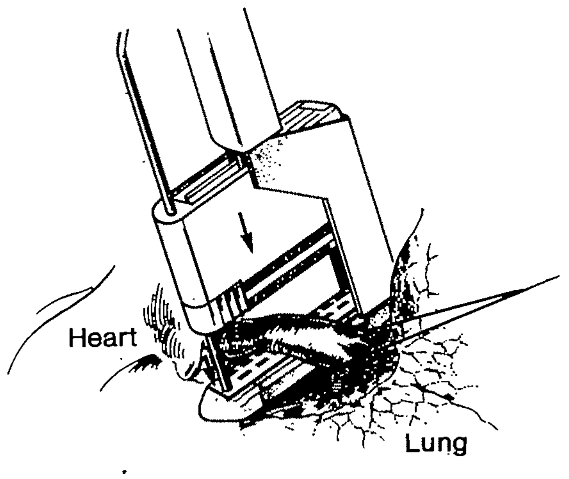

Fig 2. The stapler is in position to staple the cardiac side of the vessel. Gentle traction is placed upon the vessel using the silk suture.

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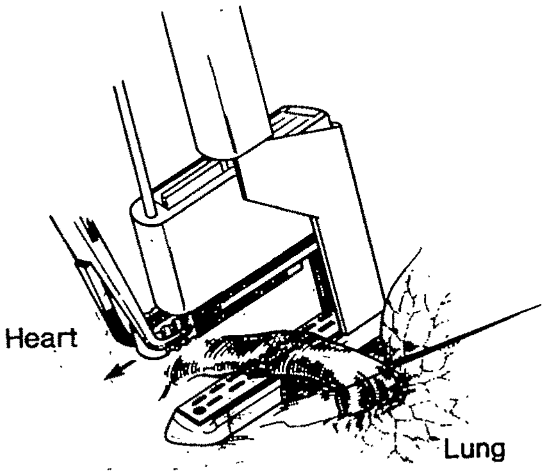

Fig 3. The spent cartridge is removed by means of a right-angle clamp.

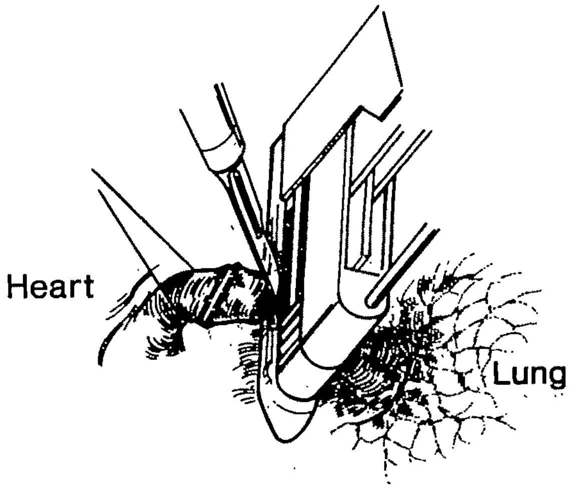

Fig 5. The second staple line has been fired and the vessel is transected with the knife supported on the anvil.

staple line, a right-angle clamp is used to remove the reloadable stapling cartridge (Fig 3). At this time, a new cartridge is dipped in saline solution to lubricate it and is placed in the upper jaws of the vascular stapler. The stapler is then shifted (Fig 4) and the 1-0 silk ligature is passed around through the jaws of the stapler to put tension on the proximal pulmonary artery or pulmonary vein. This attains a sufficient cuff of vessel distal to the clearly observable cardiac staple line. At this time, the jaws are closed and the stapler is fired; the anvil is used as a cutting surface for the second and less important distal staple line (Fig 5).

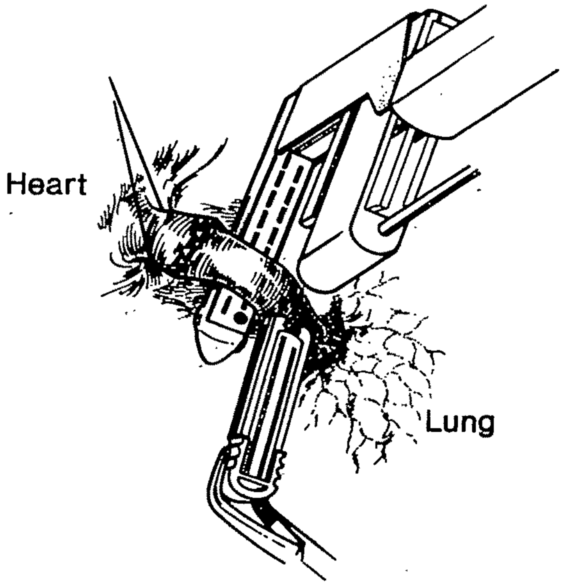

Fig 4. The stapler is repositioned and reloaded on the lung side of the vessel. This position allows careful inspection of the staple line on the cardiac side.

Comment

This technique allows the surgeon to satisfy both potential objections to vascular hilar stapling. By using the 1-0 silk suture and the reloadable cartridge, the surgeon need only place the stapler once in the application of two vascular staple lines. The first of these staple lines is placed on the cardiac side. Opening the stapling jaws allows for careful inspection of this staple line before cutting the vascular structure. The second staple line is used to permit faster and easier cutting on the anvil while visualizing the cardiac staple line.

The use of the reloadable stapler prevents the need for replacement of the stapling device after a previous staple line has been fired, thereby avoiding the "postage stamp effect." The use of the 1-0 silk ligature allows healthy traction to be placed on the vascular structure after the cardiac staple line has been applied, therefore assuring that the surgeon is better able to obtain an adequate cuff on this staple line.

We have successfully used this stapling technique in more than 100 patients undergoing pneumonectomy over a 3½-year period. We believe the technique preserves the advantages of stapling while satisfying the surgeon's need to handle the pulmonary artery and veins gently during pneumonectomy.

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Arthur Vineberg and the Internal Mammary Artery Implantation Procedure

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A summary of Vineberg's experimental pioneer work on the internal mammary artery implant is presented, together with comments on the clinical series and the difficulty in evaluating the results before the era of coronary angiography. A plea is made for recognition of the fact that an implanted internal mammary artery can arborize and communicate with the native coronary arteries.

(Ann Thorac Surg 1992;53:167–9)

It is rarely possible to pinpoint the precise moment at which a new concept is identified. The apple did not land on Newton's head. Rather, new concepts arise in prepared minds directed at specific areas of interest. For example, one might ask whatever induced Arthur Vineberg to think that an artery implanted into the left ventricular myocardium might arborize, communicate with the coronary circulation, and support life? Dr Vineberg tackled this question in the preface to a book written in his retirement years [1].

He explained that he had long had a passionate interest in coronary artery disease because it struck his father, first with a myocardial infarction and subsequently with five terminal years of angina and heart failure, all while Dr Vineberg was a young surgeon living at home with his parents. He had already learned as a medical student in the mid-1920s that coronary arteriosclerosis affected the surface coronary arteries in particular, leaving the intramyocardial arteries open. He reflected from time to time on alternate sources of arterial blood for the myocardium and had the opportunity to examine the possibilities when he was an instructor in anatomy in the early 1930s. He was attracted to the potential of the left internal mammary artery (IMA), noting the appropriateness of its size, the ease with which it could be dissected off the chest wall, and the fact that in his cadaver dissections, it would always reach the left ventricle.

Vineberg was fortunate to have trained in surgery under Edward Archibald, one of the pioneers of thoracic surgery, and his early clinical papers related to the surgical treatment of pulmonary tuberculosis. (One of Archibald's younger associates at this time was the charismatic and erratic Norman Bethune, about whom Dr Vineberg had a number of salacious stories.) Vineberg had also been schooled in scientific methodology, having acquired a master's degree in biochemistry while a medical student, and a PhD in experimental physiology (in the field of gastric secretion) while a surgical resident.

Thus, he was prepared by interest and training in the 1930s to evaluate his hypothesis that blood could somehow be brought to the myocardium through the IMA. He understood the anatomy of myocardial ischemia; he had an available expendable artery; he would not have conceived in those days that the IMA could have been surgically anastomosed to a surface coronary artery. Experimental work was required, and Vineberg was not in a position to carry this out until 1945.

In August 1946, his first report on the subject [2] was published in the *Canadian Medical Association Journal*. He presented two techniques of implanting the IMA. In one group of 6 animals, the terminally ligated artery was drawn into a prepared myocardial tunnel. In the other group of 7 animals, the IMA was not divided but freed from the chest wall until it hung like a sling. This sling was then laid in a superficial myocardial incision and held by a pleural graft or by sutures. None of the 6 hearts subsequently examined in the sling group showed any collateral circulation, and the single positive result occurred in the last animal of the tunnel group in which pink (radiopaque) Schlesinger's solution injected into the IMA flowed through the branches of the left coronary artery. When the heart was removed, the injectate was found in the aorta and it was necessary to tie off the left coronary artery at the sinus of Valsalva to keep the fluid within the coronary branches as the injection continued. The reader can imagine the excitement generated by this finding in February 1946, 4 months after the IMA had been implanted into the left ventricle. Its significance was, of course, immediately appreciated by Dr Vineberg, and he reproduced the radiographs (Fig 1) demonstrating the IMA–coronary artery communication in this single animal in several reports. In his next article [3], 27 animals had had an IMA implanted by the tunnel technique and 10 had been studied 3 to 4 months later. Two of the 10 showed a definite communication between the IMA and the left coronary circulation.

Dr Vineberg's article published in 1949 [4] documented that 8 of 49 animals that lived more than a month after operation had connections between the IMA and the coronary arteries. The experiments were segregated according to the length of IMA freed from the chest wall with the best experimental results being obtained when a minimal length of artery was isolated. No communications developed in the 14 survivors of 39 operations in

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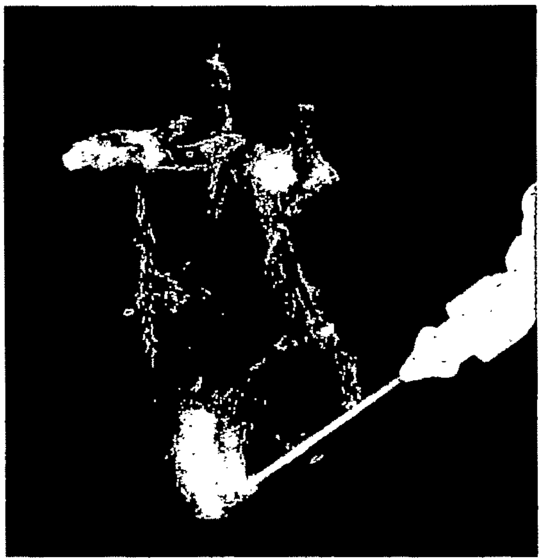


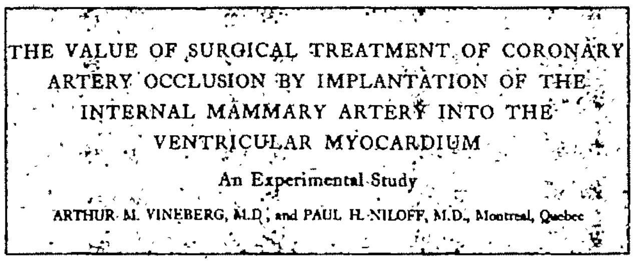
Fig 1. The radiograph included in several of Dr Vineberg's early reports showing filling of multiple coronary arteries 4 months after injection of solution into the implanted left internal mammary artery. (Reprinted from Can Med Assoc J 1946;55:117–9, by permission of the publisher.)

which the IMA was extensively freed from the chest wall (as was subsequently done in the clinical experience).

Efforts now turned to increasing the reliability of the implant procedure. Would ischemic hearts accept revascularization more consistently? In this series of experiments [5] (Fig 2), the left IMA with a bleeding sixth intercostal branch was drawn into a myocardial tunnel about 2 cm long. Subgroups underwent either concomitant ligation of a branch of the anterior descending coronary artery supplying the implant territory or ligation of the great cardiac vein close to the coronary sinus. In all survivors, the anterior descending artery was ligated at its origin 6 to 24 weeks after the implant to determine whether the implant protected them in contrast to control animals, which had only anterior descending artery ligation and no previous implant.

Thirteen of the 26 experimental animals survived anterior descending artery ligation, 9 without a trace of infarction, whereas of the 10 control animals, only 1 survived and that with an infarction. Connections between the IMA and the coronary arteries were proved anatomically in 50% of the implants.

In this report, the reader can sense Dr Vineberg's rising enthusiasm for his operation as his laboratory showed that the implant protected against infarction and death consequent to subsequent ligation of the anterior descending coronary artery. True, this protection existed only in half the experimental animals, but readers have to remember that no previous procedure had shown such benefit.



THE VALUE OF SURGICAL TREATMENT OF CORONARY
ARTERY OCCLUSION BY IMPLANTATION OF THE
INTERNAL MAMMARY ARTERY INTO THE
VENTRICULAR MYOCARDIUM

An Experimental Study

ARTHUR M. VINEBERG, M.D., and PAUL H. NILOFF, M.D., Montreal, Quebec

Fig 2. Title page from the article in Surgery, Gynecology and Obstetrics *in 1950 [5]. (By permission of* Surgery, Gynecology & Obstetrics.)

The immediate result was that Dr Vineberg, with little local support, initiated his clinical series on the basis of this experimental work. The experiments continued and techniques of gradually occluding the coronary arteries with ameroid constrictors [6] were developed, providing an experimental model of progressive coronary ischemia.

The experimental and clinical work vaulted Dr Vineberg into the role of the forerunning surgeon in treating coronary disease. Some readers may find it difficult to believe that this occurred several years before the development of coronary angiography. Dr Vineberg had pointed out that collaterals in the apical territory of the left ventricle could potentially communicate with branches of all the coronary arteries, so that anatomic localization was not essential.

The implant operation received little support among surgeons until Effler and associates [7] demonstrated angiographically the flow of contrast material down an implanted IMA and into the coronary arteries.

Comment

I have presented the bare bones of Vineberg's experimental work on coronary revascularization by IMA implantation. The clinical series grew through the 1960s until techniques for direct coronary operation were mastered. Today, implants are hardly ever done, although one could conceive of recommending this procedure to the occasional patient with inoperable surface coronary arteries. The important historical point is that the implant procedure was sometimes extremely effective, not only from the point of view of symptomatic relief, but also from that of physiologic function as demonstrated angiographically by contrast medium flowing into the myocardium from the implant. It must be acknowledged that this business of judging implant patency was not as cut and dried as readers might imagine. For example, a "patent" implant could be one in which the IMA filled with contrast medium but there was no evidence of flow through the myocardium; or there could be a faint myocardial blush with contrast medium; or there could be dramatic arborization of the implant with visualization of the coronary arteries.

Thus, the controversy over the operation's effectiveness remained even after coronary (and IMA) angiography was available. The studies were done on operative survivors, but were they typical of the other survivors? Were they restudied because of recurrent or persistent angina or as part of a clinical protocol? Neither the numerators nor the denominators were perfectly clear. There were even questions about the technique of injecting a postoperative IMA because a catheter wedged into the artery produced more dramatic filling than an injection into the subclavian artery near the origin of the IMA.

One anecdotal proof of IMA function has been described by a number of surgeons, and that is the persistence of coronary blood flow when the aorta is cross-clamped to perform a subsequent aortocoronary bypass. Some hearts keep beating despite the cardioplegic solution and stop only when the IMA is occluded.

Finally, this extraordinary procedure suffered to some extent in having Dr Vineberg as its major protagonist. It became, in an intensely personal way, his operation (he termed it the Vineberg procedure); to an extent, it became his self-imposed task to prove that the operation was effective, and this may have hindered his scientific approach. Later, he added ancillary procedures (the free omental graft, the Ivalon sponge procedure) that had little benefit but weakened his credibility.

The fact is that the implant procedure was sometimes very effective. Surgeons should recognize that Vineberg's hypothesis has been established. This highly original concept may find application some time in the future, and therefore we should not forget the procedure or its originator.

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Staging: The Key to Rational Management of Lung Cancer

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Staging is the quantitative assessment of malignant disease and allows logical groupings of patients with a similar extent of disease for prognostic, therapeutic, and analytic purposes. In bronchogenic carcinoma a stage is assigned based on size, location, and the extent of invasion of the primary tumor, as well as the presence of any regional or metastatic disease. Selecting the most appropriate treatment for a patient with bronchogenic carcinoma depends on precise staging. The extent of local invasion and presence of metastatic disease will determine the likelihood of complete resection and possible cure. Careful assessment of the history, blood chemistry, radiographic studies, bronchoscopy, mediastinoscopy, and exploration (thoracotomy) are all important staging tools. Routine radionuclide scans have no useful role when there is no clinical or laboratory evidence of metastases. The T status of a tumor is best judged by bronchoscopy and at thoracotomy. Thoracic surgeons must be familiar with the techniques available to determine T status intraoperatively and use this information when planning resection. Computed tomography of the chest has fallen short in predicting direct invasion of the mediastinum and chest wall. Cervical and anterior mediastinoscopy remain important tools in determining operability. Intraoperative assessment of node involvement determines the extent of resection and likelihood of cure.

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The importance of uniform staging criteria for lung cancer cannot be overemphasized. For each patient the selection of treatment, evaluation of operability, the need for adjuvant therapy, as well as an estimation of prognosis will all depend upon accurate staging. Equally important is the resultant ability to compare the outcome of treatment protocols from different centers.

With increasing frequency bronchogenic cancer is diagnosed without thoracotomy by sputum cytology, percutaneous needle biopsy, bronchoscopy, transbronchial needle biopsy, and mediastinoscopy. Once the diagnosis is made, it is necessary to accurately stage the tumor with the determination of size and location of the tumor (T status), the presence or absence of lymph node involvement (N status), and whether the tumor is metastatic to distant sites (M status).

Operation remains the treatment of choice for most patients with resectable non–small cell lung cancer (NSCLC). The objective of preoperative staging is to aid in the selection of patients who will benefit from resection and to exclude those patients with disease of such an extent that operation is not indicated. The information obtained from the history, physical examination, and biochemical profile will guide further staging maneuvers. Ramsdell and associates [1] presented compelling evidence that routine radionuclide scans of brain, liver, and bone have no useful role in patients who do not have clinical or laboratory evidence of metastasis to these sites. We selectively use computed tomography (CT) of the head and abdomen and nuclear bone scan in patients with (1) signs or symptoms of metastatic disease at any site, (2) a histologic diagnosis of small cell lung cancer, (3) a previous history of malignancy, and (4) high risk for resection. We employ CT of the chest selectively in the evaluation of patients with bronchogenic cancer. Its role in determining the stage and resectability is discussed below in detail.

Metastatic (M1) disease has an extremely grave prognosis. Once distant metastases are discovered the need for further staging remains controversial. The vast majority of patients with distant metastases are inoperable and incurable. In the rare case of a resectable solitary brain metastasis M1 disease is potentially curable [2, 3].

The ultimate postsurgical stage of the intrathoracic disease is determined by the histologic evaluation of the primary tumor and the presence of metastatic disease in locoregional nodes. We employ the American Thoracic Society (ATS) node map. Under this scheme intrapulmonary (stations 10 Right [R], 11 R/Left [L]) and mediastinal nodes (2, 4, 5, 6, 7, R/L and 10L) are all assigned a specific number by anatomic location (Fig 1). In this report we will outline the procedures used in our center to determine the T and N status in patients with lung cancer.

The New International Staging for Lung Cancer

The international staging system for lung cancer [4] provides a reference standard that has consistent meaning. This new staging nomenclature is intended to unify the many systems previously used around the world. The American Joint Commission on Cancer in conjunction

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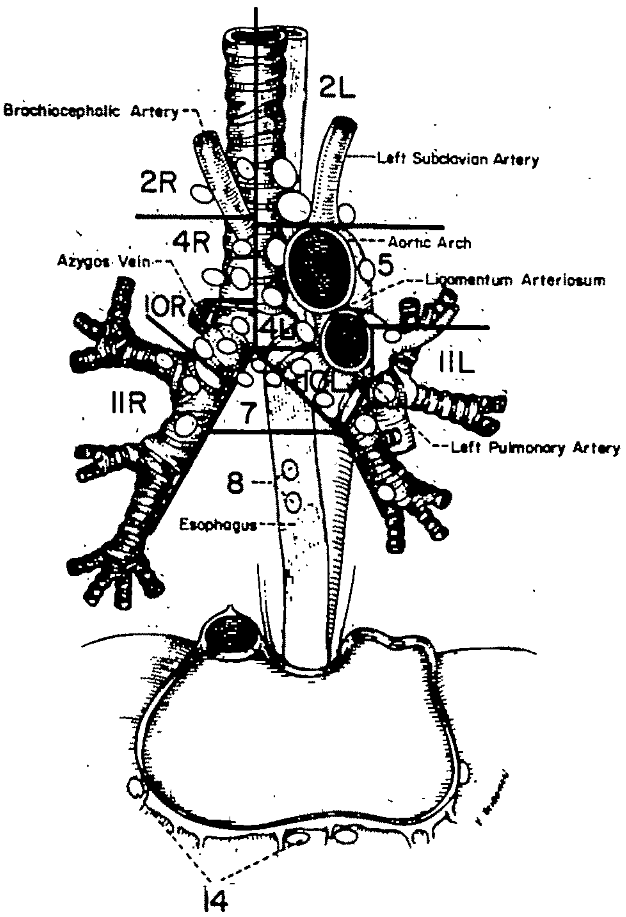

A

MODIFIED AMERICAN THORACIC SOCIETY DEFINITIONS OF REGIONAL NODAL STATIONS

Nodal Stations	Definitions
X	**Supraclavicular nodes.**
2R	**Right upper paratracheal nodes.** Nodes to the right of the midline of the trachea, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and the apex of the lung or above the level of the aortic arch.
2L	**Left upper paratracheal nodes.** Nodes to the left of the midline of the trachea, between the top of the aortic arch and the apex of the lung.
4R	**Right lower paratracheal nodes.** Nodes to the right of the midline of the trachea, between the cephalic border of the azygos vein and the intersection of the caudal margin of the brachiocephalic artery with the right side of the trachea or the top of the aortic arch.
4L	**Left lower paratracheal nodes.** Nodes to the left of the midline of the trachea, between the top of the aortic arch and the level of the carina, medial to the ligamentum arteriosum.
5	**Aortopulmonary nodes.** Subaortic and paraaortic nodes, lateral to the ligamentum arteriosum or the aorta or left pulmonary artery, proximal to the first branch of the left pulmonary artery.
6	**Anterior mediastinal nodes.** Nodes anterior to the ascending aorta or the innominate artery.
7	**Subcarinal nodes.** Nodes arising caudal to the carina of the trachea but not associated with the lower lobe bronchi or arteries within the lung.
8	**Paraesophageal nodes.** Nodes dorsal to the posterior wall of the trachea and to the right or the left of the midline of the esophagus below the level of the subcarinal region. (Nodes around the descending aorta should also be included.)
9	**Right or left pulmonary ligament nodes.** Nodes within the right or left pulmonary ligament.
10R	**Right tracheobronchial nodes.** Nodes to the right of the midline of the trachea, from the level of the cephalic border of the azygos vein to the origin of the right upper lobe bronchus.
10L	**Left peribronchial nodes.** Nodes to the left of the midline of the trachea, between the carina and the left upper lobe bronchus, medial to ligamentum arteriosum
11	**Intrapulmonary nodes.** Nodes removed in the right or left lung specimen, plus those distal to the mainstem bronchi or secondary carina (includes interlobar, lobar, and segmental nodes).
14	**Superior diaphragmatic nodes.** Nodes adjacent to the pericardium within 2 cm of the diaphragm.

B

Fig 1. (A) American Thoracic Society lymph node mapping scheme. (Reproduced from Am Rev Respir Dis 1986;147:17–20 by permission.) (B) Nodal station definitions.

with the International Union Against Cancer developed this system and proposed its implementation at the IV World Conference on Lung Cancer in 1985 (Fig 2, Table 1).

In this international classification, T1 and T2 definitions are unchanged from the American Joint Commission on Cancer staging system [5]. T3 includes parenchymal tumors that invade chest wall or mediastinum, or involve the main bronchus, but are surgically resectable by conventional criteria. T4 has been added for tumors beyond the limits of conventional surgical resection by virtue of invasion of the mediastinum or involvement of heart, great vessels, trachea, esophagus, vertebral body, or carina, or tumor associated with a malignant pleural effusion. Highly selected patients with limited carinal involvement (T4) have undergone resection for cure by sleeve pneumonectomy or carinal resection [6, 7].

The definition of N1 is unchanged from the earlier American Joint Commission on Cancer system. N2 has been revised to signify mediastinal lymph node metastasis that might be surgically resectable with curative intent (ie, ipsilateral mediastinal and/or subcarinal nodes). N3 has been added to designate lymphatic spread to nodal sites that cannot be resected with a meaningful chance of cure (contralateral mediastinal and scalene nodes) (see Fig 1).

The stage groupings have also been revised. Stage I indicates a T1 or T2 tumor with no nodal metastasis (N0). Stage II, also for T1 and T2 tumors, indicates metastases to peribronchial, lobar (including hilar) nodes (N1). It is unclear in numerous reports whether "hilar" refers to nodes inside (N2) or outside (N1) the mediastinum. The term "hilar" is inaccurate and anatomically confusing and therefore should be discarded altogether. The location of all nodes should be reported according to their specific site on the ATS node map. It is generally accepted that single-digit nodes are N2 (or N3 if contralateral) and double-digit nodes are N1. However, controversy arises with ATS nodal station 10L, which is in fact mediastinal and should be considered N2. Stage III signifies locally advanced disease and is subdivided into IIIa and IIIb on the basis of potential for complete surgical resection. Stage IIIa identifies local intrathoracic disease that has potential for complete resection. Stage IIIb designates tumor or nodal disease beyond the scope of conventional surgery (T4 or N3). Stage IV has been added to include patients with distant metastatic disease (M1).

With this new, revised TNM staging system both the designation of stage (I, II, IIIa, IIIb, IV) and the T, N, and

STAGING OF LUNG CANCER: TNM CLASSIFICATION

Primary Tumor (T)

TX	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as in a retreatment staging.
TO	No evidence of primary tumor.
TIS	Carcinoma *in situ*
TI	A tumor that is 3.0 cm or less in greatest dimension, surrounded by lung of visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.
T2	A tumor more than 3.0 cm in greatest diameter or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.
T3	A tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body, or a tumor in the main bronchus within 2 cm of the carina without involving the carina.
T4	A tumor of any size with invasion of the mediastinum or involving heart, great vessels, trachea, esophagus, vertebral body, or carina, or presence of malignant pleural effusion.

Nodal Involvement (N)

N0	No demonstrable metastasis to regional lymph nodes.
N1	Metastasis to lymph nodes in the peribronchial of the ipsilateral hilar region, or both, including direct extension.
N2	Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes.
N3	Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, and ipsilateral or contralateral scalene or supraclavicular lymph nodes.

Distant Metastasis (M)

M0	Nc (known) distant metastasis
M1	Distant metastasis present - Specify site(s)

Fig 2. The New International TNM Staging System, 1986: TNM defined.

M status are all significant indicators of prognosis (Fig 3). Each successive T, N, and M descriptor is associated with a worse prognosis, and additionally each successive stage also carries a poorer prognosis [8, 9].

Mediastinal Node Status

Mediastinal lymph node metastasis (N2, N3) is an ominous prognostic sign. Although it is generally accepted that N3 disease is beyond the scope of surgical resection for cure, there is great controversy about the significance of metastatic disease in N2 node stations. Important factors that appear to affect outcome in lung cancer patients with N2 disease are the site of the involved nodes [10, 11], number of involved nodal stations [12], and histologic cell type [12].

The goal of preoperative evaluation of the mediastinum is to identify those patients with N3 disease and exclude them from surgical consideration and select those patients with operable N2 disease. It is our opinion and the opinion of others that less than 1 patient in 5 with mediastinal nodal disease will ultimately have a complete resection [13]. The majority of these patients will not be candidates for curative resection on the basis of contralateral node involvement, extranodal extension of cancer, high paratracheal involvement, or small cell carcinoma. The recent widespread use of routine neoadjuvant therapy in this circumstance is unjustified as only pilot or phase II data exist in support of this strategy [14]. To date there are no prospective, randomized trials that show survival benefit using neoadjuvant therapy for patients with locally advanced NSCLC. For these patients the routine application of neodajuvant strategies outside a study protocol setting is at present unjustified and inappropriate.

MEDIASTINOSCOPY. The role of mediastinoscopy and CT in the assessment of mediastinal lymph node involvement is still unsettled. The most accurate prethoracotomy method of assessing N2 and N3 disease is mediastinoscopy [15–18]. Currently many centers use CT scanning of the mediastinum as a screening technique, opting for mediastinoscopy in those patients with CT-positive (>1.0 cm) mediastinal nodes [19–21]. We have found the CT scan frequently misleading, having a specificity of 88.7% and a sensitivity of only 71% [22]. We often find metastatic disease in small nodes on CT scan (<1.0 cm), and this is especially true of patients with adenocarcinoma [23] (Fig 4). We do not routinely use CT scanning to screen for nodal disease but employ mediastinoscopy as a routine part of our preoperative assessment of patient with lung cancer. We have reported its superiority over magnetic resonance imaging and CT in a prospective study of patients with bronchogenic carcinoma [22].

The Canadian Lung Oncology Group has recently completed a prospective, multicenter, randomized trial to compare the value and cost-effectiveness of preoperative chest CT with mediastinoscopy in patients with lung cancer. Patients with presumed operable lung cancer were randomized to CT or mediastinoscopy before resection and node sampling. All patients underwent surgical staging of the mediastinum before or at the time of resection. Because this study has recently been closed to accrual the data are not yet available for review.

Table 1. Postoperative 5-Year Survival in Patients With Non–Small Cell Lung Cancer

TNM Subset	Stage (Int. 1986)	Percent 5-Year Survival	
		Mountain[a]	Naruke[b]
T1 N0 M0	I	68.5	76.4
T2 N0 M0		59.0	56.9
T1 N1 M0	II	54.1	43.6
T2 N1 M0		40.0	37.6
T3 N0 M0		44.2	31.6
T3 N1 M0	IIIa	17.6	33.7
Any T N2 M0		28.8	13.7
Any T N3 M0			0.0
T4 any N M0	IIIb	3.9[c]	8.4
Malignant effusion			
Any T, any N M1	IV	1.3[c]	6.8

Sources: [a] Mountain CF. A new international staging system for lung cancer. Chest 1986;89:225a–33a. [b] Naruke T. Prognosis and survival based on the new staging system. J Thorac Cardiovasc Surg 1988;96:440–7. [c] Mountain CF. Value of the new TNM staging system for lung cancer. Chest 1989;96:47s–9s.

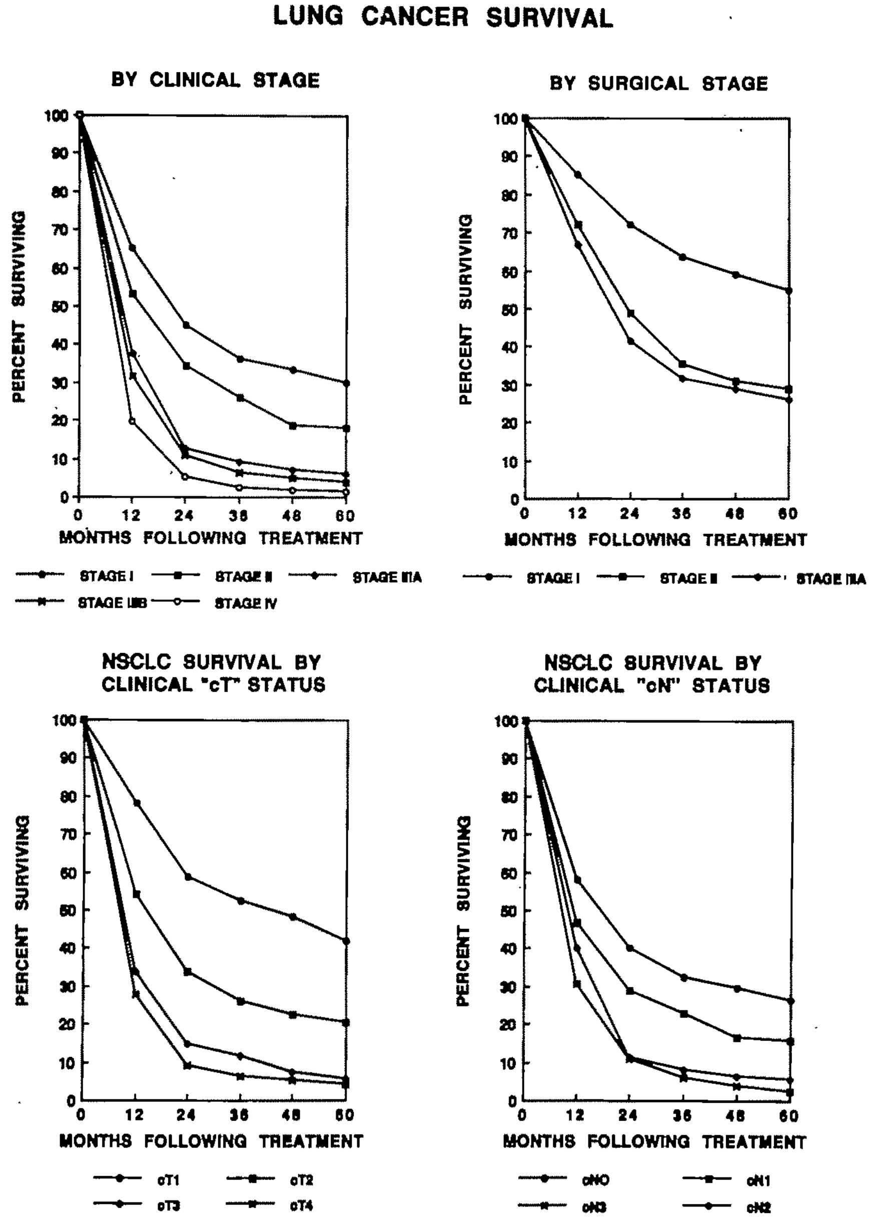

Fig 3. The New International TNM Staging System is a useful predictor of survival (survival by stage, nodal status, and tumor status is shown).

Mediastinoscopy will help select those rare patients with N2 disease who should be treated surgically [10, 11, 24]. Mediastinoscopy will also detect and identify the sites of superior mediastinal lymph node metastases and help exclude those cases from thoracotomy that would best be treated by other means. In addition, mediastinoscopy will occasionally provide the only histologic proof of small cell carcinoma and thereby prevent an unnecessary thoracotomy. The routine use of preoperative mediastinoscopy in our center has resulted in a resectability rate of thoracotomy of 93% [18].

In general, metastatic disease in superior mediastinal nodes precludes complete resection for cure, ie, the majority of such patients will not be cured by resection. This is especially true of nonsquamous cell carcinoma. There are several published series that indicate a 25% to 35% 5-year survival for patients with positive mediastinal lymph nodes when "completely" resected [25–27]. However, these data must be viewed with caution. Each of these reports were based on a small, select subset of patients with N2 disease treated surgically, and survival figures did not include unresectable cases, incomplete resections, or operative mortality. A recent review by Shields [13] concluded that less than 20% of patients with N2 disease are surgical candidates and the overall survival rate for all patients with N2 disease is between 3% and 6%.

Patients with nodal metastasis found at mediastinoscopy appear to have a worse prognosis than those patients who have a negative mediastinoscopy and are found to have resectable mediastinal node involvement at thoracotomy. Pearson and associates [11] reported the Toronto General Hospital surgical results of patients with mediastinoscopy-positive and mediastinoscopy-negative

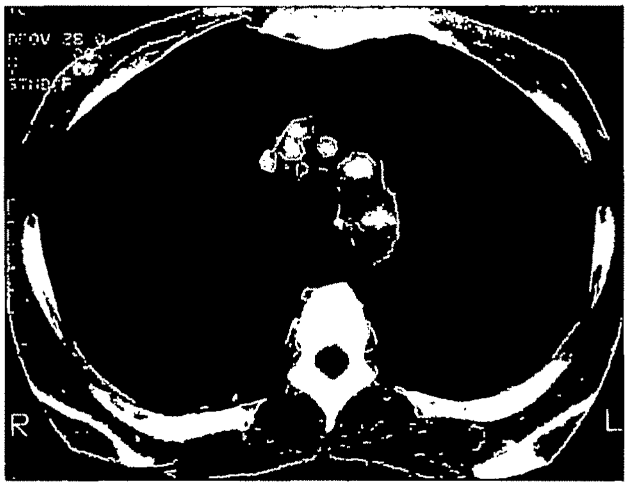

Fig 4. Computed tomography has a significant false-negative rate in determining mediastinal node involvement.

NSCLC. When operative mortality, unresectable cases, and incomplete resections were included in the survival data the absolute 5-year survival for patients with mediastinoscopy-positive lymph nodes (N2 disease) was a disappointing 9%. For those patients with a negative mediastinoscopy in whom the N2 disease was identified at subsequent thoracotomy (usually a site inaccessible by mediastinoscopy) a 24% overall 5-year survival was observed [11]. When only those patients surviving a complete resection were assessed, the survival figures were 18% for those with a positive mediastinoscopy and 35% for those who had a negative mediastinoscopy [28].

In experienced hands, cervical mediastinoscopy is safe [29]. It permits direct visualization and sampling of paratracheal (ATS nodal stations 2, 4 R/L), tracheobronchial (10 R/L), and anterior subcarinal lymph nodes (7). Anterior mediastinotomy [30, 31] and extended cervical mediastinoscopy [32] expands the assessment to include the aortopulmonary window and anterior mediastinal nodes (ATS nodal stations 5 and 6, and nodes anterior to the great vessels).

NODAL STATIONS AT THORACOTOMY. The final nodal status of a tumor can only be determined by exploration of the chest. Regardless of how careful the preoperative staging has been, accurate intraoperative staging is necessary for the purpose of planning the surgical resection. Although routine mediastinal node dissection is practiced in some centers [25], there are no prospective survival data to support this strategy over node sampling. In general we do not carry out a complete resection of all mediastinal nodes but rather sample nodes from each station. We do, however, conscientiously sample all lymph node stations not previously sampled at mediastinoscopy. We assess superior mediastinal (2, 4, R/L), subcarinal (7), subaortic (5), peribronchial (10, R/L), and intrapulmonary nodes adjacent to the proposed site of bronchial resection and submit tissue from each nodal station separately for histologic evaluation.

N1 disease cannot usually be determined until thoracotomy. The presence of tumor in N1 nodes will determine extent of resection required to adequately remove a tumor (segmentectomy versus lobectomy versus pneumonectomy). The nodes at the level of the proposed bronchial resection, either subsegmental nodes or peribronchial nodes, are submitted for immediate frozen-section pathology, and if they are found to contain tumor, a wider resection is indicated. Rarely does tumor in N1 nodes determine resectability.

For the occasional T1 lesion without nodal involvement N0) in a patient with poor pulmonary reserve, a segmental resection or a wedge resection may be used as a compromise [33]. Recent reports suggest a reasonable 5-year survival and acceptable morbidity and mortality using such lesser pulmonary resections [34]. To date local recurrence and ultimate survival rates after lobectomy versus segmentectomy or wedge resection have not been reported in a prospective, randomized trial. However, the Lung Cancer Study Group has completed a prospective study that randomizes patients with T1 N0 NSCLC to limited resection (wedge or segmental resection) or standard treatment (lobectomy). Results are expected to be published in 1991.

T Status

The status of a primary tumor, designated T by the TNM classification, is based on its size, location, and direct extension into surrounding structures and the presence of a malignant pleural effusion. History, physical examination, chest roentgenogram, and bronchoscopy are important in preoperative determination of T status.

ENDOBRONCHIAL DISEASE. The proximal extent of a tumor in the airway is determined by flexible or rigid bronchoscopy. Bronchoscopy should be carried out by the operating surgeon to fully assess the lesion, to exclude synchronous tumors, and to plan the operative approach. Tumors within a major lobar or main bronchus but greater than 2 cm from the carina are classified as T2. Tumors less than 2 cm from the carina but not involving the carina are T3 lesions. Tumors that invade the trachea or carina are T4 tumors.

Peripheral tumors or those visible at bronchoscopy but remote from the lobar bronchus are usually removed by lobectomy. Most peripheral T1 or T2 lesions are adequately dealt with by lobectomy. Occasionally tumors crossing the fissure or involving the pulmonary artery in the fissure require pneumonectomy. When the growth involves the lobar orifice or extends into the main bronchus, pneumonectomy is commonly performed. However, in this circumstance in selected patients sleeve lobectomy is an excellent alternative. Sleeve resection spares useful lung parenchyma and achieves excellent functional results and long-term survival [35]. Right or left upper lobes are most amenable to sleeve lobectomy, but sleeve resections of all lobes have been successfully performed. Computed tomographic scan and bronchoscopy will help determine the suitability of sleeve resection, but the final decision must be made intraoperatively on the basis of gross or microscopic disease at the resection margin of lobectomy. We routinely resect one complete bronchial ring proximal and distal to the tumor and perform intraoperative histological examination to ensure the bronchial margins are free of tumor. Both the operative mortality and the survival rates for sleeve resection are comparable with those of pneumonectomy [36]. Not infrequently there is local extension of the peribronchial tumor to involve the pulmonary artery. For such patients a combined bronchial and pulmonary artery sleeve resection is possible [37, 38]. However, we favor pneumonectomy if the patient has adequate pulmonary function because of the high operative risk and poor survival associated with a combination bronchoplastic and angioplastic procedure [38].

Endobronchial tumors that involve the carina or trachea are T4 lesions. Locally advanced T4 tumors are commonly associated with mediastinal lymph node metastasis and are only occasionally resectable. When the lateral wall of the trachea is invaded by a right main or upper lobe bronchus tumor, complete resection is possible using standard bronchoplastic techniques preserving the carina. Resection of bronchogenic cancer involving the carina, however, requires sleeve pneumonectomy. An operative mortality of 23% [39] for sleeve pneumonectomy has been reported. Morbidity is also high, yet experienced centers do report long-term survival of 15% to 25% [39–41].

LOCAL INVASION. The benefit of resection, the surgical approach, the need for adjuvant therapy, and the prognosis will all depend on the extent of the local invasion of a tumor. It is therefore critical to distinguish locally advanced nonresectable T4 bronchogenic cancer that invades heart, esophagus, great vessels, vertebral bodies, or trachea from resectable T3 tumors that invade parietal or mediastinal pleura, pericardium, chest wall, or diaphragm.

Invasion of the chest wall by bronchogenic carcinoma is not rare and does not imply a hopeless situation [42]. Survival after complete resection is dependent on the associated nodal status. Parenchymal and chest wall resection has resulted in substantial long-term survival in the absence of N2 disease [43].

Localized pain is helpful in determining chest wall invasion at that site [44], but this symptom is often absent. Preoperative determination of asymptomatic chest wall invasion is often difficult unless there is extensive growth through the chest wall or obvious rib or vertebral body destruction radiologically. The CT scan is of limited value in differentiating parietal pleura or chest wall invasion from peripheral tumors with visceral pleura involvement only [45] (Fig 5).

We have used preoperative radiotherapy (30 Gy) for superior sulcus tumors as described by Shaw and coworkers [46]. It is thought that irradiation will limit the extent of the tumor and enhance the success of resection. A survival rate of 31% at 5 years has been reported using this treatment regimen [47]. There are, however, no prospective or comparative studies to support this contention.

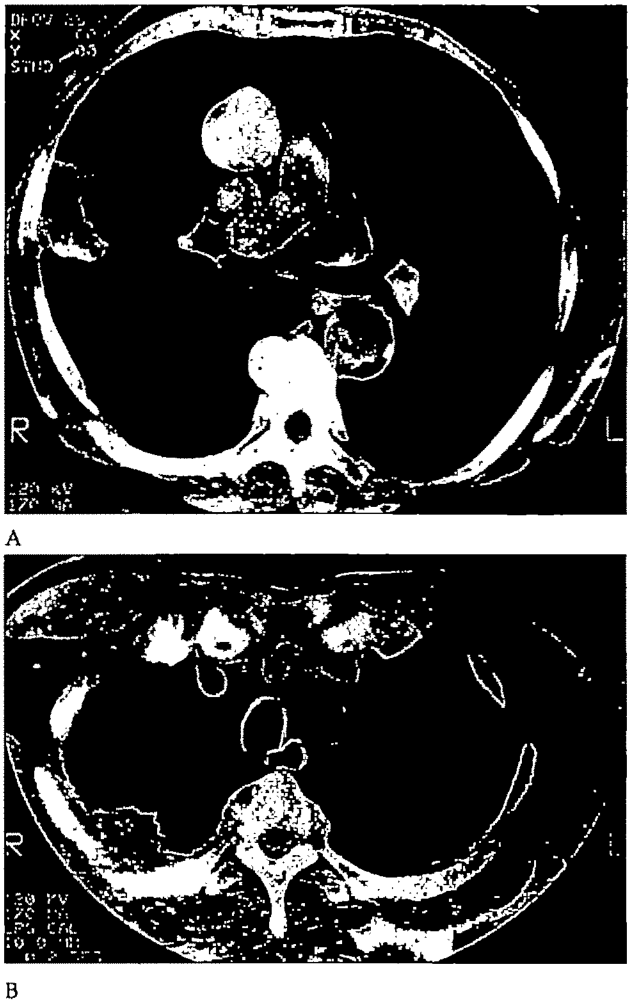

Fig 5. Computed tomographic assessment of chest wall invasion. "Indeterminate" computed tomographic scans preclude the preoperative determination of chest wall invasion.

For other bronchogenic cancers involving the chest wall there is controversy regarding the value of perioperative irradiation. In our small series irradiation appeared to provide a survival benefit [48]. However, the Mayo Clinic group did not observe any benefit with the use of preoperative irradiation [43].

At thoracotomy, the initial exploration in such patients is performed well away from the site of chest wall involvement. Before resection we sample nodal stations not previously assessed at mediastinoscopy. We routinely sample these nodes early in the operation, and if N2 disease is present we take the position that a curative resection is not likely. Usually in this circumstance the resection is terminated and the patient referred for a course of postoperative radiotherapy. If the nodal status indicates a complete resection is possible we proceed with a curative approach to the primary tumor.

Although chest wall involvement may be suspected, it is commonly first identified at thoracotomy. When a

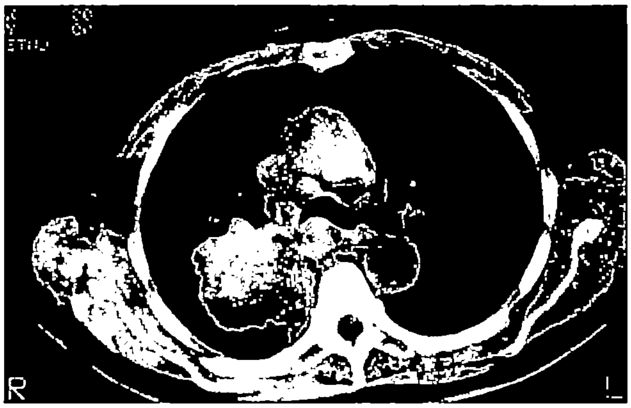

Fig 6. Computed tomographic assessment of mediastinal invasion (false-positive computed tomographic scan).

tumor is attached to the chest wall we attempt to determine whether the adhesions are inflammatory or malignant in nature by gentle manipulation and by biopsy with intraoperative histological examination. When a tumor is mobile and not fixed to the chest wall, an extrapleural resection is appropriate and is usually accomplished without difficulty. If the extrapleural plane does not develop easily or if the frozen section of the partial pleura is positive, a chest wall resection is indicated. There is no consensus for the treatment of limited parietal pleural invasion. In some centers this is treated with an extrapleural resection only [49]. Other reports suggest this procedure is inadequate [50, 51]. It is our practice to treat all T3 tumors with parietal pleural involvement by pulmonary resection and an en bloc excision of the overlying chest wall.

En bloc resection of the skeletal chest wall is accomplished by removing all areas of direct tumor involvement with a margin of at least 2 to 3 cm. We have found chest wall reconstruction is necessary in only about half of the resections, as we do not routinely remove the entire length of the involved rib(s) or the overlying chest wall, skeletal muscle, or skin nor do we resect normal ribs that are free of tumor by palpation above and below the primary growth.

Tumor extension to mediastinal structures (T4) traditionally cannot be resected for cure, but some surgeons have reported resection with reconstruction for palliation [37, 38, 40]. Occasionally gross mediastinal invasion can accurately be predicted by CT scan, and exploration to confirm the tumor is "unresectable" is not justified. However, T4 status cannot be accurately determined preoperatively when a central lesion is seen on CT scan to lie in apposition to the mediastinal structures. Radiographic criteria such as the loss of the mediastinal fat pad and the extent of mediastinal or great vessel contact are helpful but cannot predict mediastinal invasion with accuracy [52]. Patients with such central lesions should be explored if the mediastinum is free of tumor at mediastinoscopy and there is no evidence of extrathoracic disease (Fig 6). A wide en bloc resection of the mediastinal pleura, pericardium, phrenic nerve, or aortic adventitia is warranted. Occasionally a small portion of the vena cava can be resected and repaired primarily. Although resection of the great vessels and reconstruction has been described, operative mortality is high (17%) and long-term survival is poor [38, 40, 53, 54]. When limited vertebral body involvement is identified intraoperatively, resection of a small portion of the vertebral body is possible provided the costovertebral foramen is not involved [55].

PLEURAL EFFUSION. A tumor associated with a malignant pleural effusion is staged T4 and incurable by resection. However, only patients with a verified malignant effusion should be denied resection. Repeated cytologic evaluation of aspirated fluid, pleural biopsy, and pleuroscopy may all be necessary to substantiate the diagnosis of a malignant effusion.

Summary

The understanding of lung cancer has been advanced by the application of universally accepted staging criteria. Staging not only allows for comparison of treatment protocols but is fundamental in the practical management of each patient with bronchogenic carcinoma.

Selection of the best treatment for patients with lung cancer depends on its precise stage. Preoperatively metastatic disease is assessed by radiographic studies. Computed tomography, however, has fallen short in predicting tumor in the mediastinum and chest wall. Cervical mediastinoscopy remains an important surgical tool in determining operability. Knowing the level of nodal disease is critical in determining operability. We generally favor resection only in a select group of N2 cases with ipsilateral non–small cell bronchogenic cancer that are deemed totally resectable at mediastinoscopy.

Findings at bronchoscopy help establish the endobronchial T status. With preoperative bronchoscopy the surgeon can determine operability and plan the level of resection. T status as defined by local direct tumor extension into surrounding structures in the mediastinum or chest wall is best judged at thoracotomy. In general we are much more aggressive with tumors with local extension than those with nodal disease.

Intraoperative surgical staging of mediastinal lymph nodes is pivotal in determining the value of resection in T3 tumors involving chest wall. Knowing the status of intrapulmonary nodes allows the surgeon to plan the extent of resection. Intraoperative frozen section assessment of these regional lymph nodes is mandatory.

The importance of accurate surgical staging cannot be overemphasized. Not only does it permit analysis of primary and adjuvant treatment protocols, but it allows determination of prognosis and selection of appropriate treatment for each patient.

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Benign Tumors of the Lung

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CORRESPONDENCE

Nonhemic Prime in Cardiopulmonary Bypass

To the Editor:

The valuable editorial on erythropoietin that was published in *The Annals* recently [1] appeared to imply that the introduction of a nonhemic prime for cardiopulmonary bypass, producing intentional hemodilution—a major advance in the development of open heart surgery—was the contribution of Dr Cooley and his associates in Houston. I wish to correct this misunderstanding. Although the Houston group became late advocates of this technique, the credit for this work—which enabled open heart surgery to expand rapidly and safely on a scale not previously envisaged—must go solely to Nazih Zuhdi of Oklahoma City.

Until February 1959, pump oxygenators had been uniformly primed with large volumes of fresh heparinized blood obtained from donors on the day of operation. In that month, Dr Zuhdi and his colleagues were the first to introduce a citrated banked blood prime [2], which greatly facilitated preparation for open heart surgery. By coupling this innovation with the design and development of a low-volume reservoir heart-lung machine (which had the additional advantage of incorporating a volume-reducing heat exchanger allowing internal hypothermic perfusion), the quantity of (banked) blood required for the procedure was greatly reduced.

The final step (or "quantum leap") was taken by Dr Zuhdi on February 25, 1960, when, after his extensive laboratory studies in 1959, he introduced into his clinical cardiac surgery program the use of a totally nonhemic pump oxygenator prime using 5% dextrose in water, inducing intentional hemodilution [2–4]. This advance, coupled with the small-capacity pump oxygenator, probably did more than any other single innovation to enable open heart operations to be performed in the numbers to which we have become accustomed today. Before nonhemic priming was introduced, it was estimated that not more than 50 to 75 open heart procedures were performaed in the United States each day.

Foote, Long, Gadboys, Dewall, and their respective colleagues soon followed this lead, but it was not until the April 1961 issue of the *Journal of the American Medical Association* that the Houston group—after direct communication with Dr John Carey of the Oklahoma City group—discussed the potential benefits of a nonhemic prime, and not until November of that year that they described some pilot experimental studies [5]. Their first report of the clinical use of nonhemic prime appeared in November 1962 [6]—some 2 years after Zuhdi's initial report and almost 3 years after his initial clinical case. By that time, the employment of nonhemic primes, intentional hemodilution, and banked citrated blood for blood loss replacement was already an everyday occurrence in many active centers across the nation.

Dr Zuhdi's leading role in this field was described by Dr Clarence Dennis in his laureate address to the American Society of Artificial Internal Organs in 1985 and was recognized by the American College of Cardiology in the Milestones of Cardiology in 1989. His contributions are possibly even more remarkable as both the experimental laboratory and clinical studies were carried out while he was in private cardiothoracic surgical practice in a community hospital in Oklahoma City.

Truly important advances in any field of medicine are uncommon. The introduction of a nonhemic prime and intentional hemodilution for open heart surgery is one such advance. It is important that the individual (or individuals) responsible for the advance should receive due credit and recognition. In this case, those of us who followed have been reaping the rewards of Dr Zuhdi's endeavors for the past 30 years on a scale unimagined in the pre-Zuhdi era.

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Reply

To the Editor:

We certainly appreciate Dr Cooper's letter drawing attention to the historical contributions of Dr Zuhdi of Oklahoma City to the concept and application of nonhemic primes for cardiopulmonary bypass. In our editorial, our reference to the 1962 report by Cooley and associates was meant to cite a reference to this methodology and its application in the conduct of cardiopulmonary bypass. We certainly did not intend to imply that Dr Cooley and his associates introduced the concept or originated its application.

We thank Dr Cooper for bringing forward to the readership's attention the important contribution of Dr Zuhdi and his associates to the field of hemodilution for cardiopulmonary bypass, and for his historical and chronological review of their original introduction of this concept.

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Combined Superior-Transseptal Approach to the Mitral Valve

To the Editor:

Dr Berreklouw and his colleagues [1] have given an excellent report with illustrations of the combined superior-transseptal approach to the mitral valve.

We have used this approach in 8 patients, of whom 4 had reoperations. Mitral valve replacement and repair were done in 6 and 2 patients, respectively. The mitral valve procedure was combined with tricuspid valve repair in 2 patients, coronary artery bypass grafting in 2 patients (along with use of retrograde

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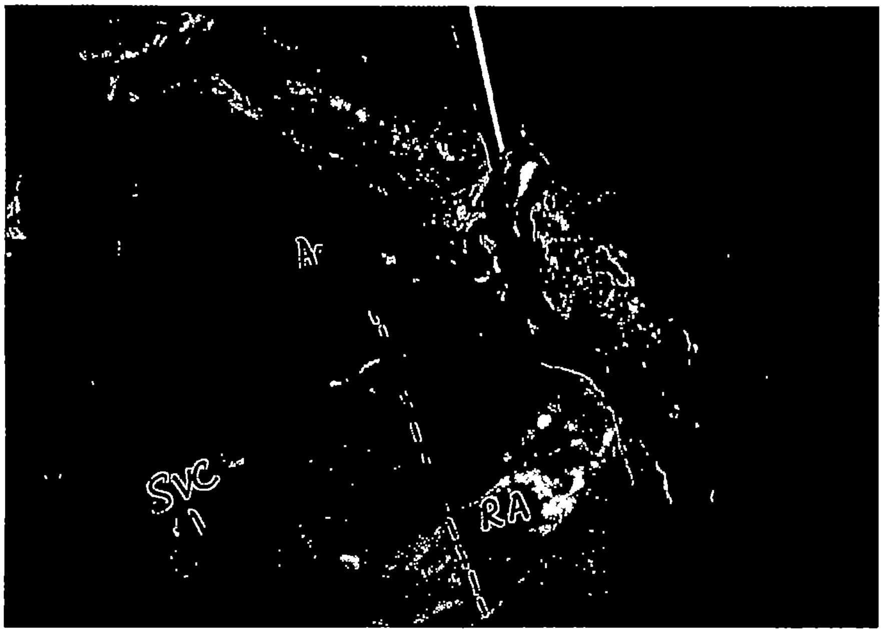

Fig 1. Sinus node artery arising from right coronary artery (RCA) and traversing in the groove between aorta and right atrial (RA) appendage. The incision (shown by dotted line*) transects this artery.* (SVC = *superior vena cava.)*

cardioplegia), and correction of tetralogy of Fallot in 1 patient. Our procedure is similar to that described by Dr Berreklouw and his colleagues. We fully agree with them in that exposure of mitral valve is excellent and no retraction instrument is necessary. Postoperatively we share a common experience with no incidence of conduction defects or intraatrial shunting related to the approach.

One of our senior authors has described the efficacy of the superior approach [2] to the mitral valve. Combined superior and transseptal approach further improves the exposure of the valve, especially in small left atrium and in reoperations. Additional indications, in our opinion, for using this approach for mitral valve exposure would be when a concomitant tricuspid valve operation is contemplated; when retrograde coronary sinus cardioplegia is used in a patient undergoing coronary artery bypass grafting who needs an additional mitral valve operation; and in patients having atrial fibrillation with a fast ventricular rate, in whom this incision may be of help in reducing the reentry phenomenon and thereby indirectly help in controlling the ventricular rate.

Good exposure of the mitral valve using this approach is particularly helpful in two situations: (1) It is much easier to excise the prosthetic valve in reoperations for prosthetic valve dysfunction. (2) With this approach the mitral valve, along with the subvalvar apparatus, is readily accessible, making an accurate repair possible.

Our main concern in using this approach is damage to the sinus node artery. If we consider the anatomy of sinus node artery with respect to the incision (Fig 1), it will be clear that there is transection of the sinus node artery when the transseptal incision is extended on to the roof of the left atrium. Damage to the sinus node artery is thought to be an important cause of early and late dysrhythmias in the atrial switch (Mustard's) procedure [3]. There were no instances of conduction defects in the study by Berreklouw and associates as well as in our experience in the immediate and early postoperative course. In their report, Dr Berreklouw and associates have not given the long-term follow-up of these patients as regards incidence of late dysrhythmias. Our longest postoperative follow-up is 4 months. Hence, we do not know the incidence of late dysrhythmias, which can occur due to chronic changes in the sinoatrial node after damage to sinus node artery [3]. We are thus not overzealous in using this approach and have restricted its use where the exposure of the mitral valve may be difficult, as in reoperations and small left atria.

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Bronchoscopic Appearance After Single-Lung Transplantation

To the Editor:

We would like to draw the attention of your readers to the hyperemic appearance of the donor bronchial mucosa after single-lung transplantation.

A 57-year-old man underwent right-sided single-lung transplantation for emphysema. His initial postoperative course was uneventful. Immunosuppression was commenced with rabbit antithymocyte globulin, cyclosporine, and azathioprine. Postoperative analgesia was effected using continuous paravertebral block with bupivacaine [1]. Before extubation at 6 hours postoperatively, fiberoptic bronchoscopy confirmed satisfactory bronchial mucosa. On the fifth postoperative day, he had an episode

Fig 1. Bronchoscopy 6 weeks postoperatively shows a well-healed bronchial anastomosis with hyperemia of the donor bronchial mucosa.

of acute rejection manifested by right pleural effusion and leakage from the thoracotomy wound. The effectiveness of the paravertebral block allowed exploration and resuturing of the thoracotomy wound without further analgesia or anesthesia. This episode resolved with intravenous doses of prednisolone. Bronchoscopy at 2 weeks postoperatively confirmed satisfactory healing. Transbronchial biopsy showed no evidence of rejection. Bronchoalveolar lavage did not reveal evidence of infection. Oral prednisolone was commenced. His condition was stabilized with low-dose prednisolone, cyclosporine, and azathioprine, and he was discharged home 3 weeks after operation.

He remained very well with improved exercise tolerance and excellent respiratory function parameters. Routine bronchoscopy at 6 weeks showed a well-healed bronchial anastomosis (Fig 1) with hyperemia of the donor bronchial mucosa distal to the ridged appearance of the anastomosis. The lack of rejection was confirmed by transbronchial biopsy and lack of infection by bronchoalveolar lavage. A repeat bronchoscopic examination at 3 months confirmed the same picture, with the patient remaining in excellent condition.

We believe that the hyperemia has resulted from sympathetic denervation of the bronchial vasculature. This should not be misinterpreted as evidence of rejection, and this report should serve as a cautionary tale for the unwary. Rejection should be confirmed by transbronchial biopsy.

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Fine-Needle Aspiration Biopsy

To the Editor:

Based on 188 patients with suspected pulmonary malignancy who underwent fine-needle aspiration biopsy, Colquhoun and associates [1] conclude that "although accuracy can be quite high, the actual influence on patient management may be much less." Their conclusions resulted in part from obtaining nondiagnostic specimens from fine-needle aspiration biopsy in 53 (28.2%) of their 188 patients. What eventually happened to the 38 patients with nondiagnostic biopsies who did not undergo thoracotomy is not stated.

The yield of positive aspiration biopsies is related to the methods used as well as to the experience of the operator. Several suggestions to improve the yield of fine-needle aspiration biopsy may be helpful. The cytologist should examine the aspirate near the operating suite (5 to 10-minute wait) so that a nondiagnostic yield can be followed by repeated aspirations until diagnostic material is obtained. The needle, under suction, may be manipulated with both hands if an assistant holds the suction syringe. The needle should be "jabbed" several times into the suspect area during aspiration. Biplane fluoroscopy with a single image intensifier that can be rotated for anteroposterior and lateral visualization leaves adequate room for the operator to position himself or herself efficiently [2]. The plea is worth repeating that all personnel in the suite wear aprons and dosimeter badges that are monitored monthly by the Radiology Department.

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Reply

To the Editor:

We appreciate Dr Taber's comments with regard to our results and agree that the technique of needle biopsy is most important and is well described in his letter. The method used in our study was essentially the same as that described by Dr Taber. Furthermore, Dr Rosenthal is a very experienced cytopathologist. Thus, despite the best efforts of an experienced team, the results of percutaneous fine-needle aspiration biopsy failed to establish a correct diagnosis on many occasions. For this reason, we believe percutaneous fine-needle aspiration biopsy adds little to the preoperative workup of a patient who is otherwise a surgical candidate. In such cases, either a positive diagnosis or a negative diagnosis requires confirmation or therapy by thoracotomy. Therefore, in our opinion, percutaneous fine-needle aspiration biopsy might best be reserved for establishing a diagnosis of malignancy so that nonoperative therapy can be instituted in patients who are not surgical candidates or in patients with suspected infectious disease.

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ Twenty-eighth Annual Meeting of The Society of Thoracic Surgeons, Orlando, Florida—February 3–5, 1992

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

■ Second International Lung Transplant Symposium—Update 1991, Laguna Niguel, California—February 12–14, 1992

This symposium is sponsored by Cedars-Sinai Medical Center. For information on this meeting, contact Department of Continuing Medical Education, Cedars-Sinai Medical Center, at (213) 855-5547.

■ First International Symposium on Diseases of the Aorta, Tokyo, Japan—February 24–26, 1992

For information on this meeting, contact Japan Convention Services, Inc, Nippon Press Center Building, 2-1, 2-chome, Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.

■ Pathophysiology & Techniques of Cardiopulmonary Bypass, San Diego, California—February 27–March 1, 1992

This meeting is the Twelfth Annual San Diego Cardiothoracic Surgery Symposium. For information on this meeting, contact the Cardiothoracic Research & Education Foundation, PO Box 23220, San Diego, CA 92193; or telephone (619) 541-1444 (facsimile: (619) 541-1447).

■ American College of Surgeons, Orlando, Florida—March 22–25, 1992

For information on this meeting, contact American College of Surgeons, 55 Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

■ General Thoracic Surgery, Las Vegas, Nevada—April 2–3, 1992

This postgraduate course is sponsored by the American College of Chest Physicians and the University of Nevada School of Medicine. For information, contact ACCP, Division of Education, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Twelfth Annual Meeting of the International Society for Heart Transplantation, San Diego, California—April 2–4, 1992

For information on this meeting, contact ISHT, 435 N Michigan Ave, Suite 1717, Chicago, IL 60611; or telephone (312) 644-0828.

■ One Hundred Twelfth Annual Meeting of the American Surgical Association, Palm Desert, California—April 6–8, 1992

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Forty-first Annual Meeting of the American College of Cardiology, Dallas, Texas—April 12–16, 1992

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ Seventy-second Annual Meeting of the American Association for Thoracic Surgery, Los Angeles, California—April 27–29, 1992

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Thirty-eighth Annual Meeting of the American Society for Artificial Internal Organs, Nashville, Tennessee—May 7–9, 1992

For information on this meeting, contact ASAIO Registration, 2200 North Federal Highway, Suite 201, Boca Raton, FL 33431-7710.

■ Fourteenth World Congress of The International Society for Heart Research, Kobe, Japan—May 10–14, 1992

For information on this meeting, contact Makoto Nagano, MD, Secretariat, XIV World Congress of ISHR, Department of Internal Medicine, Jikei University Medical School, Aoto Hospital, 6-41-2 Aoto, Katsushika-ku, Tokyo 125, Japan.

■ The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Chicago, Illinois—June 8–10, 1992

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Cardiostim 92, Nice, France—June 17–20, 1992

For information on this meeting, contact Dr J. Mugica, Centre Chirurgical Val d'Or, 16, rue Pasteur, 92211 St-Cloud Cedex, France; or telephone (33) 1.46.02.70.72 (facsimile: (33) 1.46.02.05.09).

■ Eighteenth Annual Meeting of The Western Thoracic Surgical Association, Kauai, Hawaii—June 25–27, 1992

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Sixth Annual Meeting of The European Association for Cardio-Thoracic Surgery, Geneva, Switzerland—September 14–16, 1992

For information on this meeting, contact Symporg S.A., 108, route de Frontenex, CH-1208 Geneva, Switzerland; or telephone 41-22 786 37 44 (facsimile: 41-22 786 40 80).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 26–30, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

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SITUATIONS AVAILABLE

Thoracic/vascular surgeon needed to join prominent, active 3-man group in desirable suburban community in greater NY metropolitan area. Excellent opportunity for well-trained, highly motivated individual. Recent graduate preferred. Possible academic affiliation. Please respond with CV.

Please respond to Box 404. 404I/C

Cardiothoracic and vascular surgeon, board eligible or certified, to join 2-man private practice in Ft. Lauderdale, Florida. Send CV.

Please respond to Box 542. 542L/E

BC/BE cardiovascular and thoracic surgeon wanted to join busy two-member group in Fort Lauderdale, Florida. Recent US medical graduate preferred.

Please send CV to I. Tabry, MD, 2773 NE 37th Drive, Fort Lauderdale, FL 33308 [(305) 561-9781 after 9:00 PM]. 570H/A

Cardiovascular and thoracic surgeon to join established 3-man private practice in mid-South. Practice includes thoracic, cardiac, and vascular surgery. Must be board certified or eligible in thoracic and cardiovascular surgery. Prefer candidate who has recently completed his/her training. Please respond with curriculum vitae.

Please respond to Box 580. 580H/A

Thoracic-peripheral vascular surgeon: BC/BE to join busy 32-physician multispecialty group practice in central Florida. Competitive salary incentive and benefit package with early partnership. Five-hundred-bed hospital located less than ½ mile from office. Attractive central Florida lake country community is abundant in water sports, fishing, hunting, and outdoor sports. One and one-half hours to either coast.

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Cardiothoracic surgeon, BE/BC, to join busy 1-man private practice in mid-Michigan. Excellent opportunity. Salary leading to partnership. Please send CV and references.

Please respond to Box 601. 601J/C

Cardiovascular and thoracic surgeon, BC/BE in thoracic surgery, to join active cardiac, thoracic, and vascular practice with academic affiliation in large Midwest city. Transplant experience desired. Reply with CV.

Please respond to Box 608. 608J/A

Cardiovascular and thoracic surgeon, board certified or board eligible, to join a rapidly expanding single hospital practice in the upper Midwest. Salary leading to partnership. Please respond with curriculum vitae.

Please respond to Box 609. 609J/C

Private practice opportunity in New York. Adult and pediatric cardiac surgery only. Postgraduate training in pediatrics a plus but will seriously consider all qualified applicants. Please respond with CV.

Please respond to Box 611. 611J/C

Excellent practice opportunity for well-mannered, technically accomplished CV surgeon in California wine country. Growing 2-surgeon practice in beautiful semirural area close to San Francisco—great family environment. Prefer young surgeon with 2–5 years' experience, ABTS board certified.

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Assistant cardiac surgeon for an expanding program in its third year in the Tri-State area of Ohio, Kentucky, and West Virginia. The selected individual will be in charge of first assist in the operating room and share the responsibility of assessing the preoperative and postoperative cardiac surgical patient. The average load is 200 patients per year and increasing. The necessary qualifications include a valid WV license and board eligibility in thoracic surgery. Working experience in cardiac surgery preferred.

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Cardiac surgeon: recently trained, board eligible or certified cardiac surgeon interested in joining an expanding practice in the Tri-State area of Ohio, Kentucky, and West Virginia.

Please inquire at (304) 525-1414 or send CV and letters of recommendation to Tri-State Cardiac Surgery, Inc, 2828 First Ave, Suite 100, Huntington, WV 25702. 641L/B

Cardiovascular surgeon: excellent practice opportunity for recently trained BC/BE cardiovascular surgeon with initiative. Work to focus on cardiac surgery, but vascular coverage necessary. Midwest location. Salary/full partnership negotiable. Please send CV.

Please respond to Box 642. 642L/B

Cardiothoracic and vascular surgeon, board certified/board eligible, to join a 3-man practice in the Midwest. Salary leading to full partnership. Please send curriculum vitae.

Please respond to Box 643. 643L/B

Cardiothoracic surgeon, BE/BC, wanted to join established practice in mid-Michigan group of two. Ninety percent of practice is adult surgery and ten percent is general thoracic surgery. Respond with CV and names of references.

Please respond to Box 644. 644L/E

The Division of Thoracic and Cardiovascular Surgery at the University of New Mexico School of Medicine in Albuquerque is seeking applications for a full-time faculty position at the Assistant Professor level for July 1992. We are looking for an individual with excellent surgical skills, strong interest in research and teaching. The candidate must be board eligible or certified. We offer a competitive salary. This is an excellent opportunity for an individual interested in academic achievements as well as a good clinical experience.

Please forward curriculum vitae and three letters of recommendation to Jorge A. Wernly, MD, Chief, Division of Thoracic and Cardiovascular Surgery, University of New Mexico Medical Center-ACC2, Albuquerque, NM 87131. An affirmative action/equal opportunity employer. 646L/C

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Please respond to Box 648. 648L/E

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Please send curriculum vitae to Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015. 652A

Cardiovascular and thoracic surgeon—board eligible/certified to join a noncardiac surgical practice located in the mid-Atlantic states. Respond with CV and details of experience. Recent graduate preferred.

Please respond to Box 654. 654A/C

Cardiovascular and thoracic surgeon wanted to join a busy expanding private practice group in the Midwest. Excellent program with large number of experienced invasive cardiologists. Applicant must be BE/BC. Prefer recent graduate. Training in heart transplantation desirable. Please reply with curriculum vitae.

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Please respond to Box 656. 656A/C

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Please respond to Box 662. 662A

SITUATIONS WANTED

Board-certified cardiovascular surgeon, 48, university trained, wishes to relocate. Interested in group practice. CV and references upon request.

Please respond to Box 573. 573H/A

Cardiothoracic surgeon, 37, US graduate, university residencies, cardiopulmonary transplantation fellowship. Three years of busy academic adult cardiothoracic surgery practice including transplantation and arrhythmia surgery. ABS, ABTS certified. Fellow ACS, ACCP. Member STS, ISHT. Publications. Wishes to relocate, interested in private or academic group practice.

Please respond to Box 599. 599J/A

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Please respond to Box 632. 632K/A

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Please respond to Box 633. 633K/A

FELLOWSHIPS

Fellowship in vascular surgery—The Deborah Heart and Lung Center is currently seeking qualified applicants for a Vascular Fellow position.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 651A

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Submit complete curriculum vitae to John C. Baldwin, MD, Professor and Chief, Cardiothoracic Surgery, Yale University School of Medicine, 333 Cedar St, PO Box 3333, New Haven, CT 06510. Yale University is an affirmative action/equal opportunity employer. 660A

Cardiothoracic surgical fellowship. Available July 1, 1992, to June 30, 1993. One year noncredited appointment available to persons completing general surgery residency to assist in the preoperative management, surgery, and postoperative management of cardiothoracic surgical patients.

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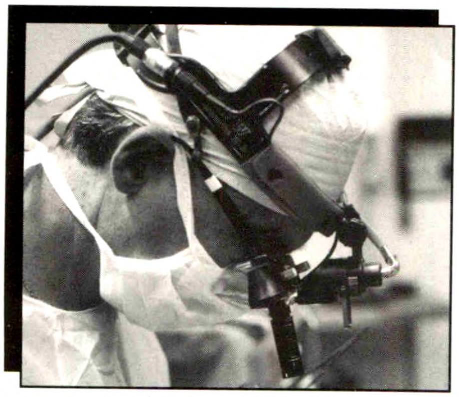

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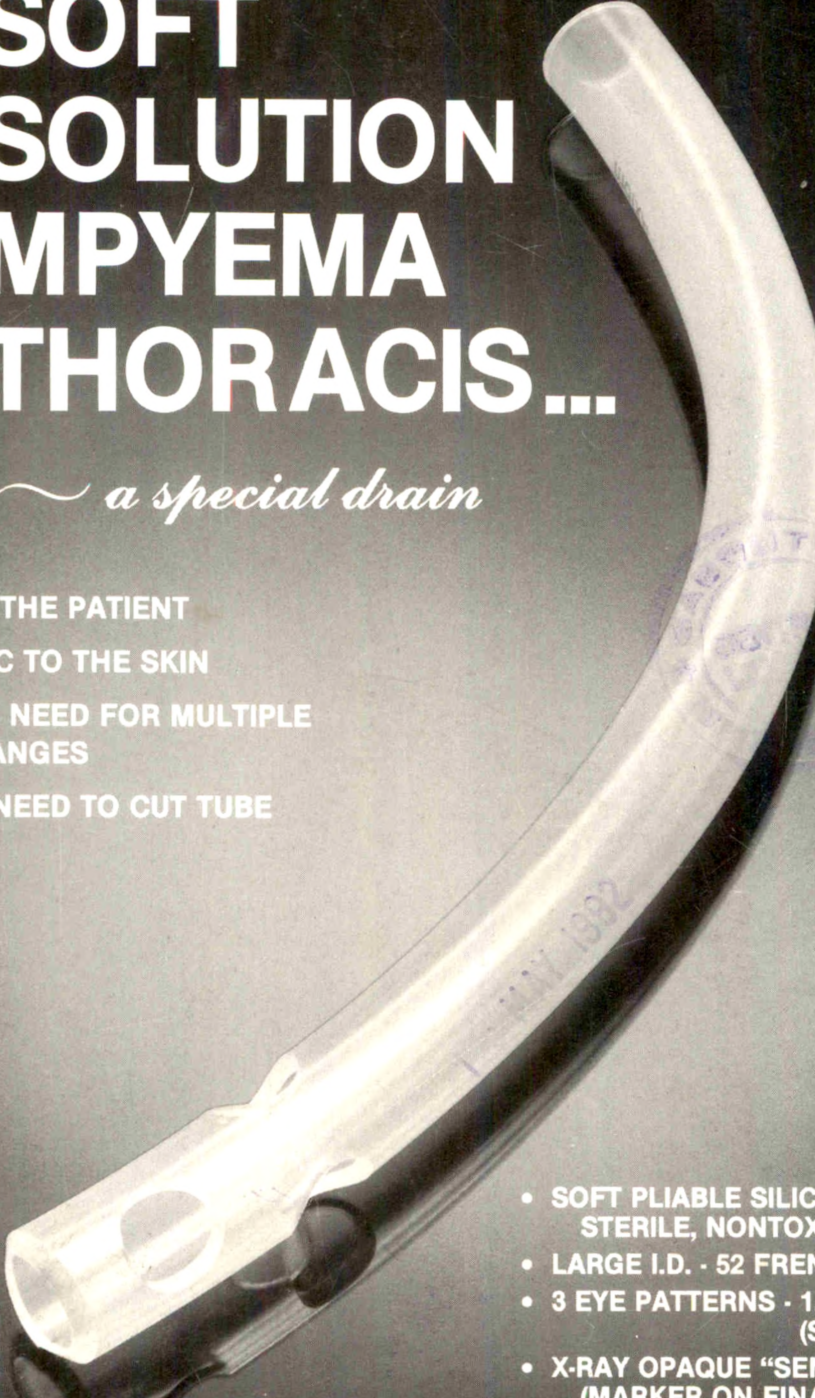

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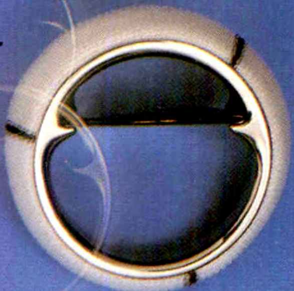

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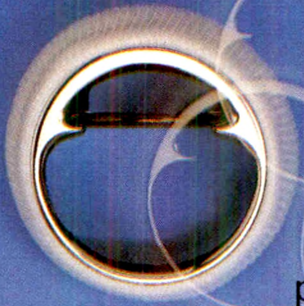

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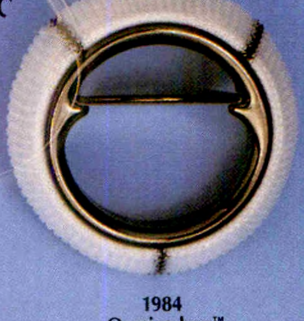

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February 1992

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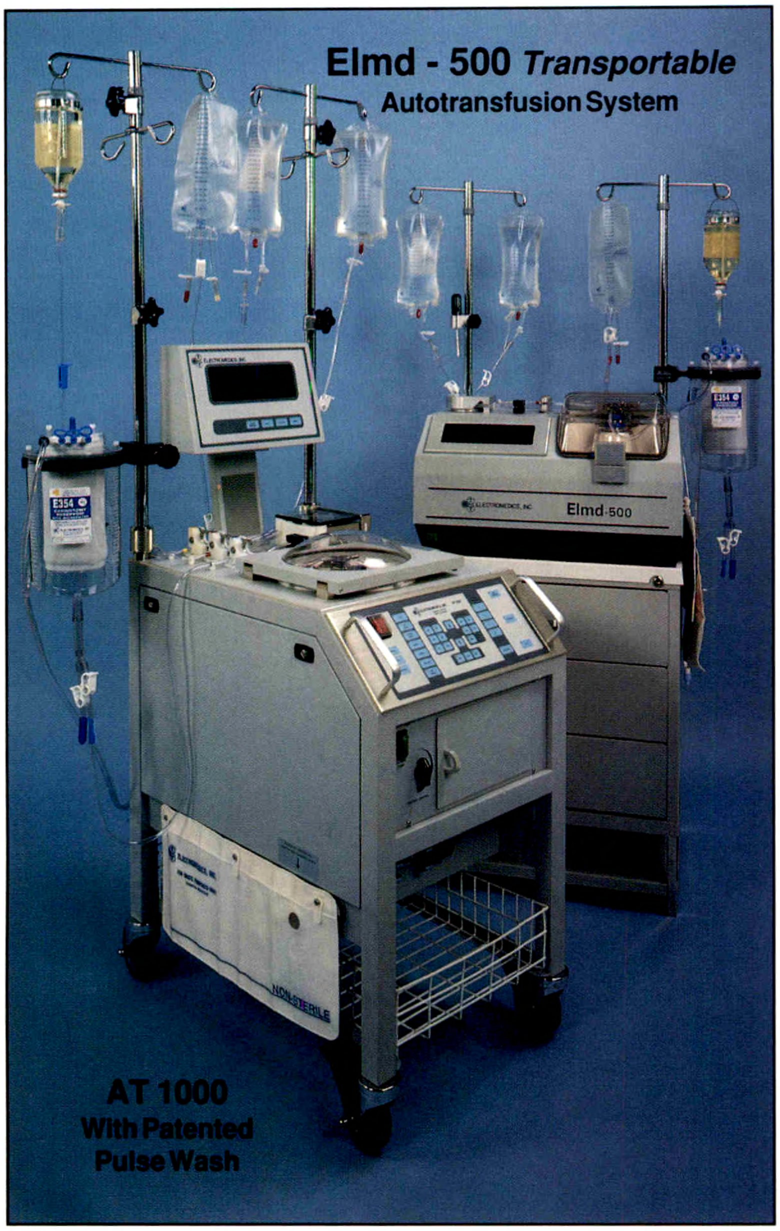

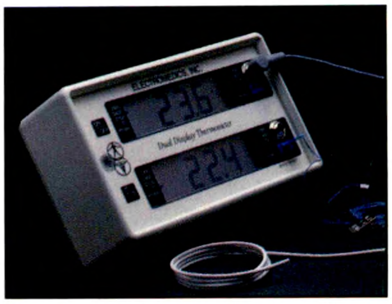

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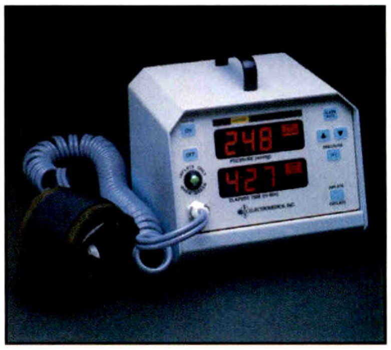

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Carpentier-Edwards® Duraflex™ Models 6625LP and 6625-ESR*-LP
Mitral Low Pressure Bioprostheses
For Single Use Only

Design

As compared to other types of prostheses, preserved porcine bioprostheses exhibit certain potential advantages: the need for long-term anticoagulation may be minimized; and although the durability of porcine bioprostheses is a limiting factor in long-term evaluation, tissue degradation is usually progressive and symptomatic, thereby permitting detection with proper annual follow-up in person with a physician, and elective intervention when necessary.

Models 6625LP and 6625-ESR-LP Mitral Carpentier-Edwards® Duraflex™ Bioprostheses are comprised of porcine aortic valves that have been preserved in buffered glutaraldehyde and then mounted on flexible frames. Glutaraldehyde is shown to both reduce the antigenicity of porcine xenograft valves and increase tissue stability.

The frame is designed to be flexible at the orifice as well as at the commissures. The compliance of the stent's commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The flexibility of the orifice is intended to reduce the loading shock at the base of the leaflet. The flexible orifice concept is based on the physiology and mechanics of natural heart valves and reported experience with implantation of unstented homografts.

The lightweight frame is made of Elgiloy,** a corrosion-resistant alloy, chosen because of its superior spring efficiency and fatigue-resistant characteristics.

The metal frame is covered with a porous, knitted polytetrafluoroethylene cloth to facilitate tissue ingrowth and encapsulation. The inflow orifice is contoured to support the right coronary cusp of the porcine valve. The commissure supports are not equidistant to conform to the anatomical configuration of the porcine aortic valve. The suture ring has a soft, silicone-rubber insert that is covered with a porous, seamless polytetrafluoroethylene cloth. The compliant nature of the suture ring facilitates coaptation between the valve and an often irregular or calcific tissue bed.

The porcine aortic valves are fixed in buffered glutaraldehyde, and then mounted on cloth-covered frames. After mounting, the valves are tested *in vitro* to ascertain their competency and flow characteristics. After final inspection, the valves are sterilized, rinsed, and then transferred into fresh glutaraldehyde and packaged under aseptic conditions.

Low Pressure Fixation

In vitro studies by Broom, et al., advise that to maintain optimum mechanical properties in the fixed porcine aortic leaflet tissue, the full collagen waveform or crimp originally present in the relaxed fresh tissue should be retained. In addition, these studies show that the collagen waveform is sensitive to alteration at fixation pressures as low as 4 mm Hg. Edwards CVS Division has developed a process to fix porcine aortic valves at a hydrostatic pressure less than 4 mm Hg to minimize alterations in the collagen waveform of the aortic valve tissue. Low pressure fixation of Carpentier-Edwards Duraflex™ bioprostheses is intended to increase the clinical durability of these valves; however, data regarding Carpentier-Edwards Duraflex™ bioprostheses are insufficient to demonstrate that durability has been increased by this preparation technique or that calcification has been reduced.

Indications

Bioprostheses are indicated for use in patients suffering from valvular heart disease. Mitral valvular heart disease is a condition involving any of the following: obstruction of the heart valve or stenosis; leakage of the valve, known as regurgitation or insufficiency; and combination of the two, sometimes referred to as mixed disease or combined lesions.

Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease, and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia.

Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards Duraflex™ bioprosthesis is intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on maintenance hemodialysis.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after carefully evaluating the short- and long-term risks and benefits to the patient, and considering alternative methods of treatment. The overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of tissue valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (See Clinical Experience).

Careful and continuous medical follow-up (at least annually by a visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. Please refer to the most recent Clinical Experience attachment for data on anticoagulation relating to these valves. The appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards Duraflex™ bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across Carpentier-Edwards® Duraflex™ bioprostheses could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in a sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C (50°F) and 25° C (77° F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact with the eyes, seek medical attention.

Surgical Precautions

The models 6625LP and 6625-ESR-LP Duraflex™ mitral valves are unapproved for indications other than mitral valve replacement.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards Duraflex™ bioprostheses, compiled from the literature and from reports received through the complaint handling system in accordance with the United States (federal) regulations establishing Good Manufacturing Practices section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period, and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards Duraflex™ bioprostheses to calcification as compared to other commercially available porcine valves.

See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

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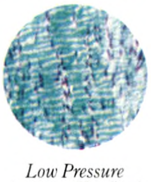

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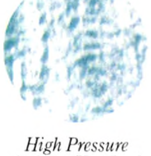

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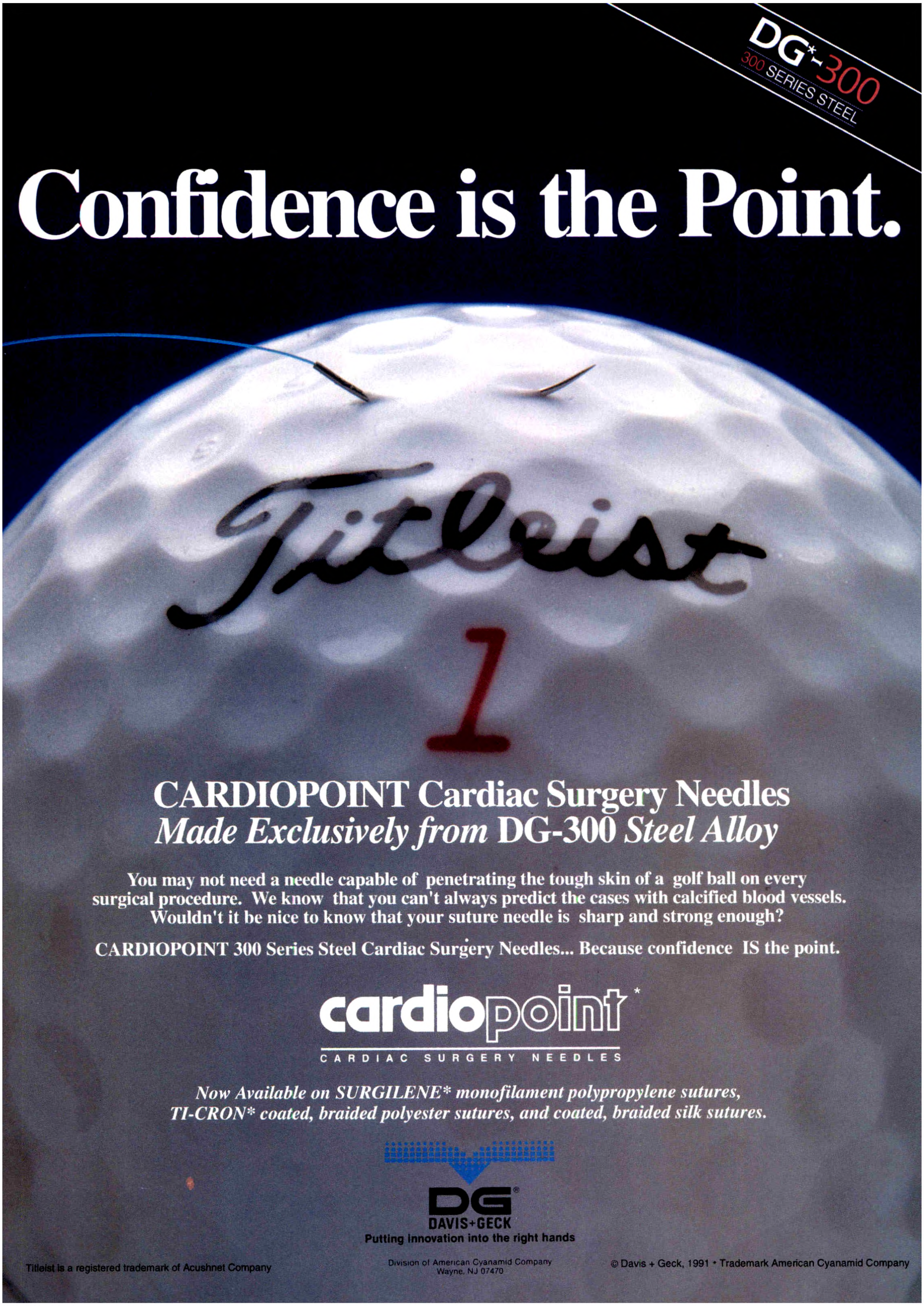

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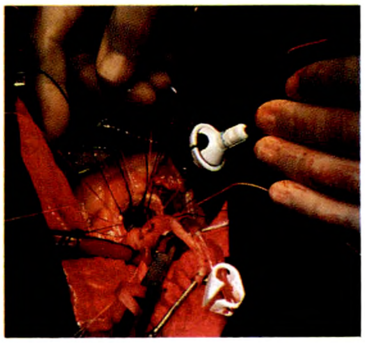

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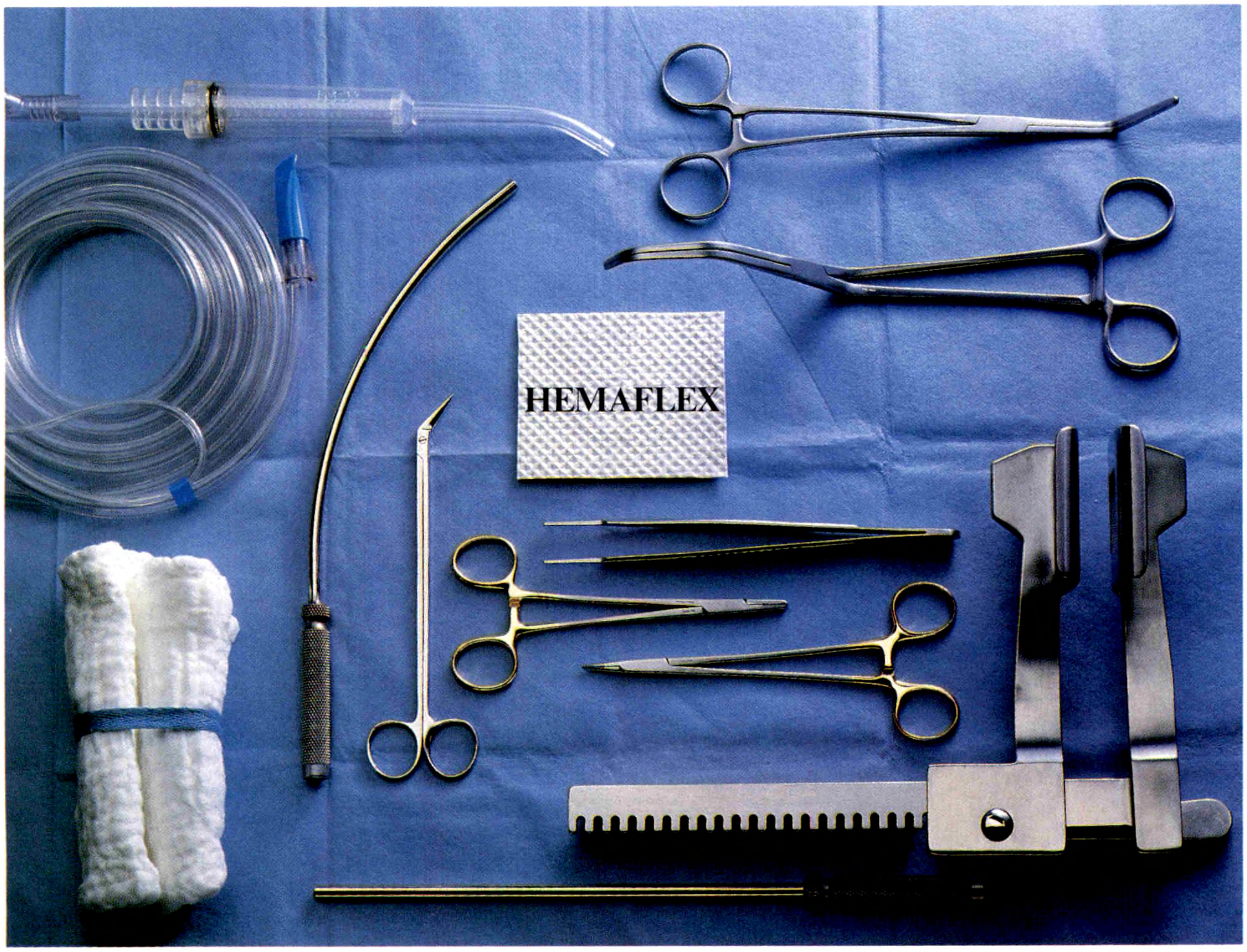

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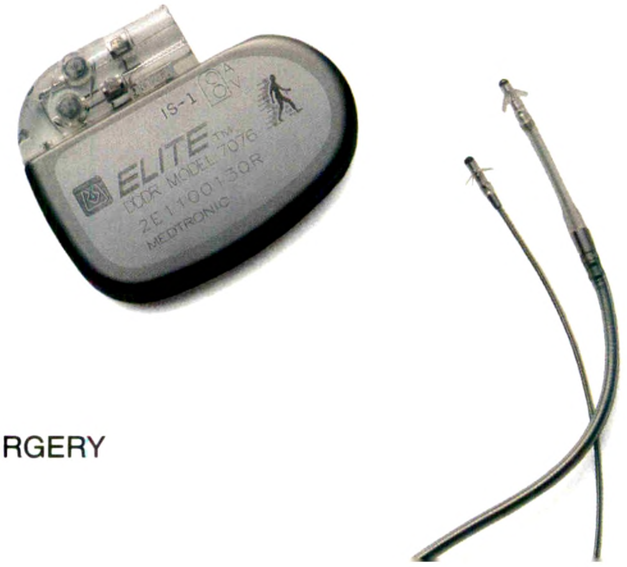

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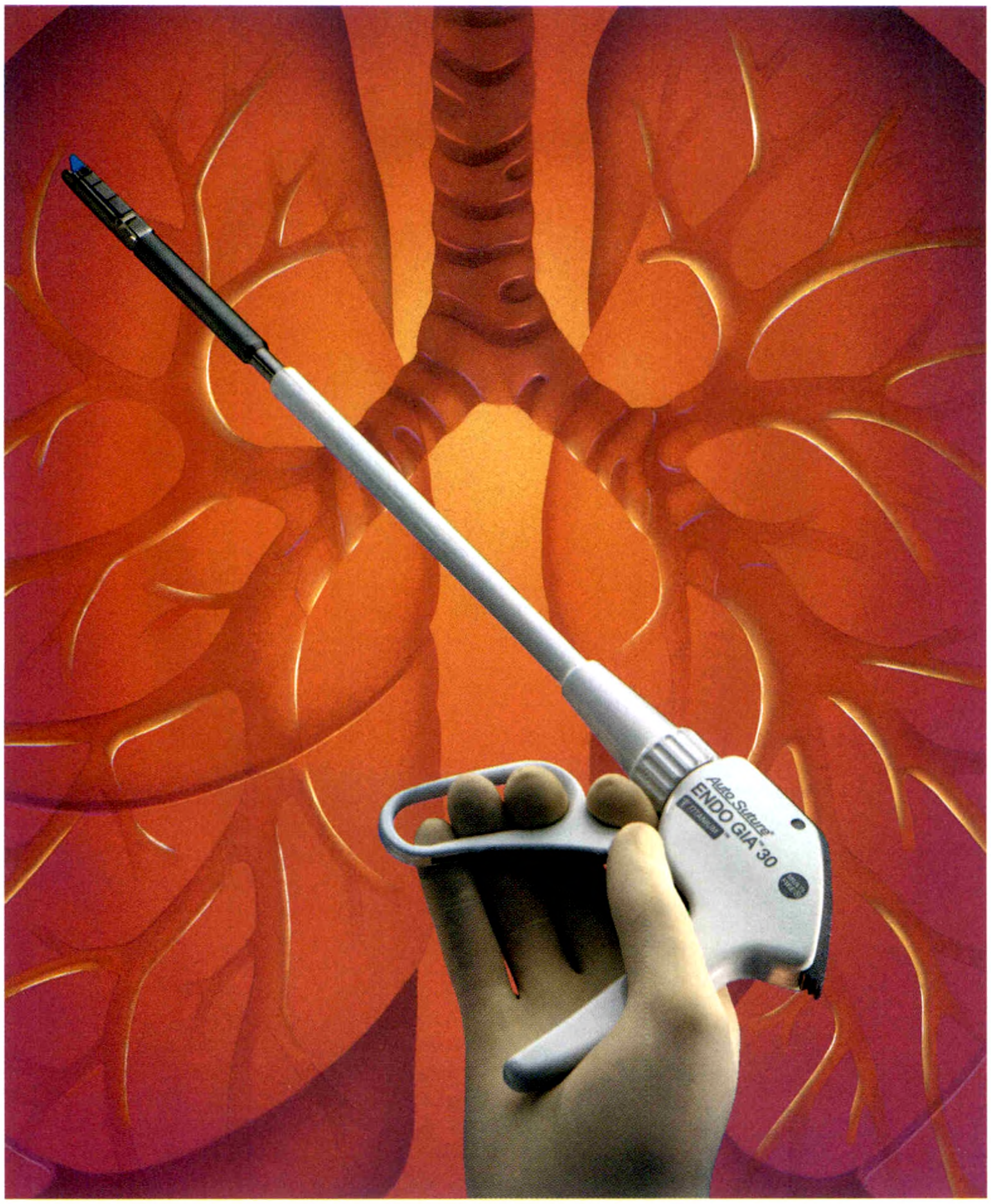

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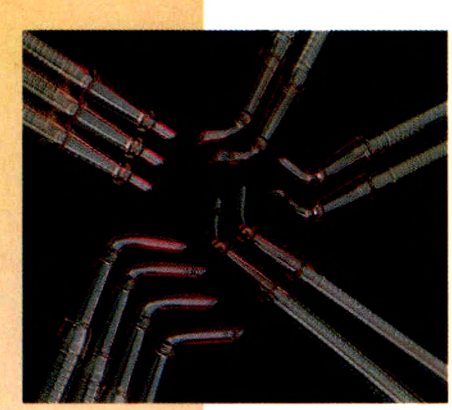

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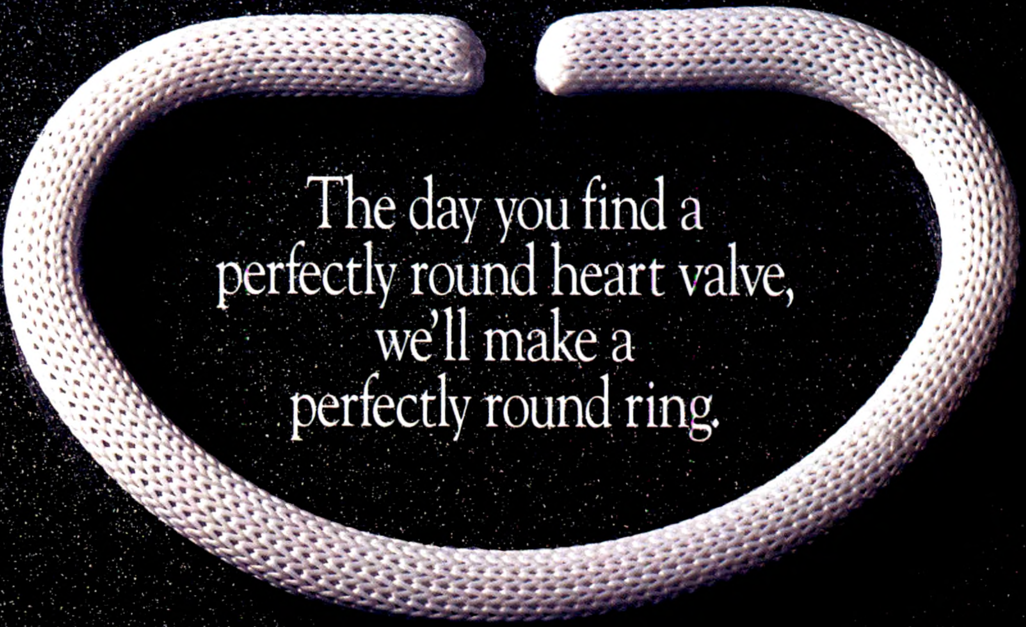

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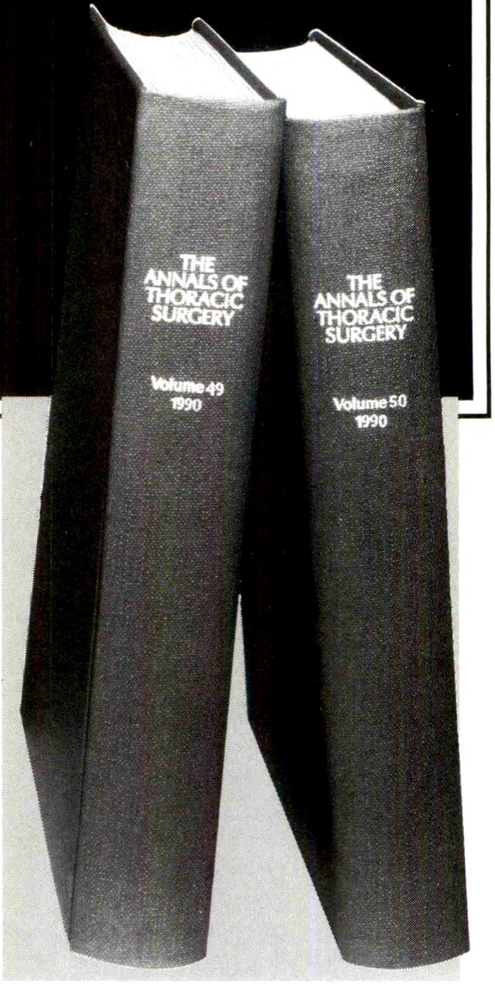
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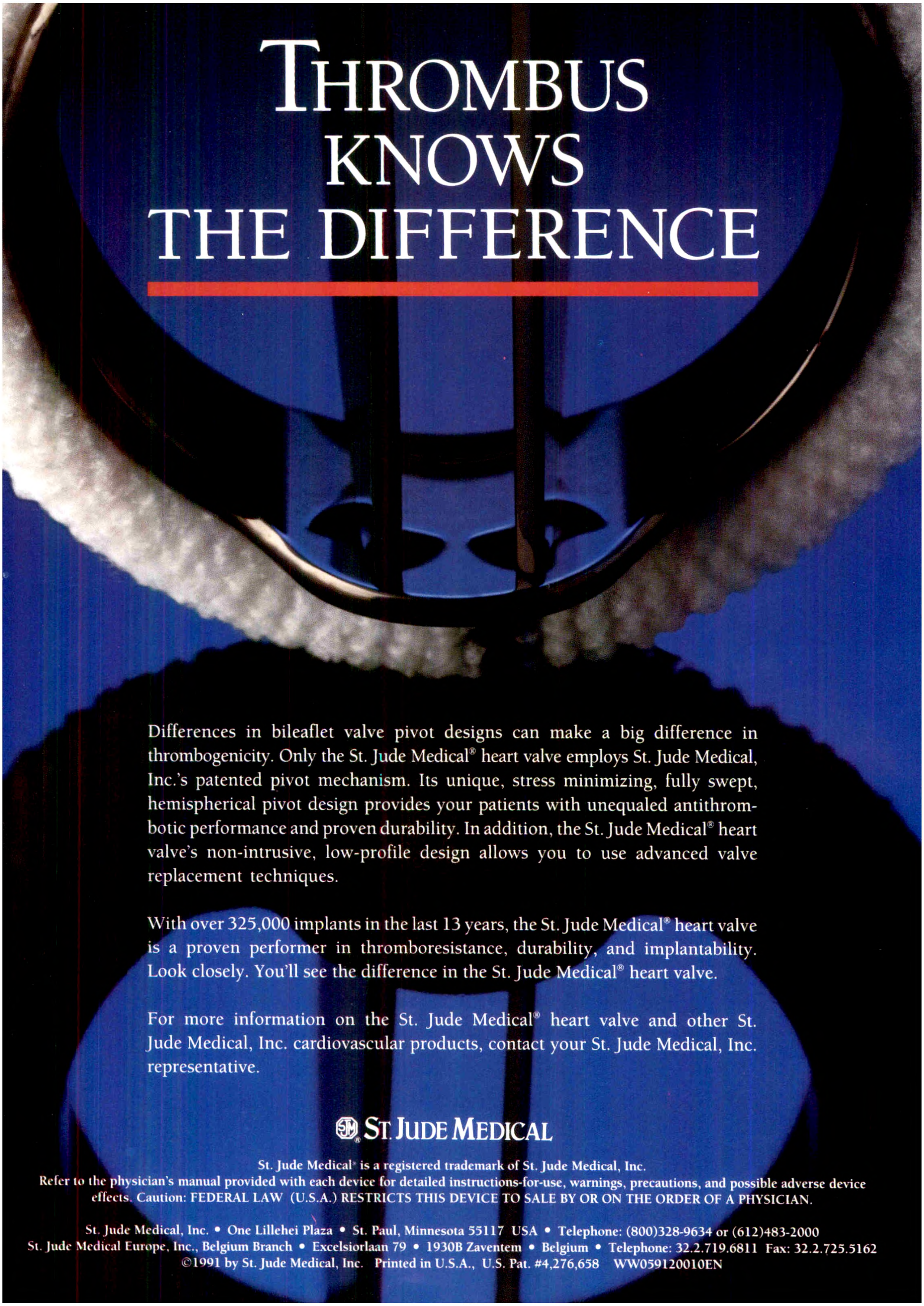

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The Different Drummer, the Double Agent, and Future Dilemmas in Bioethics

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The Arena of Bioethical Discourse

Over the past 20 years or so, bioethics has evolved from a relatively perfunctory set of written rules to an arena of intense discussion and heated debate. The risk to patients posed by physicians who test positive for the human immunodeficiency virus [1], the conception of a child for the specific purpose of providing a grown sister with bone marrow for treatment of chronic myelogenous leukemia [2], and the use of advance directives for end-of-life health care [3] have all been full-color cover stories for national magazines in the past 3 months. The newsworthiness of many of these issues brings into sharp focus the intimate relation between bioethics and other areas of public and private life, like health policy, biotechnology, and the legal system [4].

Policy, technology, and the law are influenced by bioethics, but the reverse is also true: these areas have profoundly affected the way in which we think about and practice ethics. Some of these interactions are salutary, and some are not. A few recent changes of direction in ethical thinking should stir serious concern, because they may threaten the foundations of our profession. If it is worthwhile to preserve professional integrity, and I believe it is, it may be useful to consider some of the philosophic origins of our decision-making processes—our medical ethics.

Two fundamental principles of bioethics about which I am particularly concerned are autonomy and beneficence. Autonomy means "self rule": the right of every person to control his or her own body, to choose his or her own values, and to act on them. Beneficence is to do what is good for the patient. The minimum level of beneficence is nonmaleficence: first, do no harm. But the principle of beneficence goes far beyond this simple minimum, requiring positive actions to achieve what is good for the patient. Beneficence in the care of patients was expressed for centuries as paternalism, the notion that the physician should do what is medically good, regardless of the patient's preferences or values, but in recent decades, this tradition has been gradually replaced by a greater emphasis on respect for autonomy [5].

The threats to autonomy and beneficence come from many sources, the most prominent being economic pressures generated by the dizzying rise in health care costs over the past 25 years, exhorting the physician to conserve the public and the corporate dollar [6]. Another is a philosophic movement away from respect for individual values toward a greater emphasis on social values [7]. A third threat is the development of astounding new technologies, which has filled some physicians with hubris that does not mesh well with a contemplative, caring approach to patients [8]. I metaphorically refer to these dangers in the title of my talk: the different drummer and the double agent.

The discipline of ethics deals with the way we make choices that will enable us to achieve the good life. One of the fundamental quests of philosophy is to describe what is the good life [9].

Autonomy

> If a man does not keep pace with his companions, perhaps it is because he hears a different drummer. Let him step to the music which he hears, however measured or far away.
>
> Henry David Thoreau [10]

Henry David Thoreau's masterwork, *Walden*, was written more than a hundred years ago, yet stands even today as a vital symbol of the American spirit. The caption above exhorts us to be mindful of and to respect our individual and different values. Thoreau had his own vision of the good life, which was different from that of most of his contemporaries. A thread running through all his works was a plea to leave people be, to allow each man to seek his own truth and his own vision of the good life. Each of

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us hears his own different drummer, and we must respect our individual paces, as we respond to the music that guides our own lives.

An Illustrative Case

I recently encountered a case that raised questions about who should make medical decisions in the face of conflict.

A 6-year-old boy, John Keating, had numerous congenital malformations, including a myelomeningocele (for which he had a reparative operation during infancy), which left him without control of bladder and bowel, severe kyphoscoliosis, Arnold-Chiari malformation with hydrocephalus (for which he had a series of ventriculoperitoneal shunts), a large head accentuating his abnormally small face, and visual and hearing impairments that left him both blind and deaf. Difficulty swallowing led to poor nutrition, but a gastrostomy a year ago improved his nutritional state. He also had cyanotic congenital heart disease. An early death was predicted when he was a newborn, and several times since then.

When he first saw John, the cardiologist, Dr Mondavi, was immediately struck by his piteous appearance. He was extremely small: at 6 years of age, his weight was still less than 15 pounds, and his length less than 27 inches. He had severely restricted range of motion of all extremities, his cervicothoracic vertebral column was fixed in moderate extension, and he could lie only on his sides unless propped up. He had a barrel chest and appeared to have very little movement of accessory chest wall muscles. His cyanosis was severe, oxygen saturation just greater than 0.60. He did not appear to respond to either sound or visual stimuli, but cried when handled.

Over the past year, his cyanosis had increased markedly, and his hemoglobin level rose from 15 to 18 g/dL. Cardiac evaluation demonstrated the presence of double-outlet right ventricle with severe tetralogy of Fallot.

John's case was presented to the pediatric cardiac medical-surgical conference. In the ensuing discussion, opposing positions were taken by various physicians. One argued that this child has severe disabilities and could never participate in any meaningful way in family life or other activities. His life span is markedly limited, and his physical disabilities, particularly the chest wall deformities, substantially increase the risk of any operation. In fairness to this severely limited child who has already suffered greatly, no operation should be done, and it is we, not the parents, who should make that decision. In the great scheme of things, our limited resources would best be spent elsewhere.

Another physician argued that the patient is after all a human being, and, like any other patient, should be offered only two options, a shunt or a corrective operation. A third opinion was that John is wanted and loved by his family, so any judgment regarding the value of his life or his current or potential contribution to the family or society has to be left to his parents; we should go no further than describing the risks and benefits of all the options, including shunt, correction, or no operation.

Dr Mondavi made an appointment to meet with th Keatings in his office. What should he say to them?

Who Should Decide?

Many ethical issues are raised by this case. What in fact i best for the child? Has he suffered enough already? I maximal extension of life truly in his best interests? Hov should the quality of his life with or without operation b weighed in making these judgments? Who should decid what is best for John? Are our limited health care resources wisely expended for the very limited gains possible for this child?

These are important questions, and allow no eas answers. The issue of whether the physician or th patient is the proper locus of decision-making directl runs into the tension between the two principles at th core of medical ethics: autonomy and beneficence. Thes principles are usually mutually supportive, but only whe the value systems of the physician and the patient ar congruent.

We live in a morally pluralistic society: Roman Catholic working in the same office with Orthodox Jews, fundamentalist Christians serving on town council with vocal politically active homosexuals, highly educated, well-to-do professionals living a few blocks from public housing projects for the indigent. Even the two broades divisions of humanity, men and women, may hav widely differing views of the way the world works differences that were dramatically illustrated in the recen Clarence Thomas-Anita Hill hearings.

Although achievement of the good life is the ultimat objective of all ethical discourse, these dichotomou groups represent a wide range of value systems, wit enormously differing views of what constitutes the goo life. The different value systems of participants in medica decisions make the good or the right choice different fo each of us, and inevitably may lead to conflict.

Ethical reasoning is basically aimed toward the resolution of conflicts in medical choices. Conflict in a medica decision can be resolved in three ways: by one part forcing the other to accept its decision, by persuasiv conversion of one participant to the other's view, or b negotiation through established procedures [11].

The search for ethical answers is guided by reason When reason fails, resolution can be achieved by threat o harm to person or property, that is, by force. Force can b manifested at the personal level, for example, by assault, theft, or fraud, or at the public level, for example, by passage of laws that mandate acceptance of outcomes no freely chosen. Examples in health care might include incomplete explanation of available therapeutic options, effectively forcing the patient to accept a predetermined treatment, so-called weak paternalism [5], or passage o laws mandating the use of generic drugs or participation in certain health care plans [12].

The use of force is the antithesis of reason, a result o the failure of reason. It cannot be ethically justified, except when used in defense against another's use of force [13]. In an open and free society, there are some issues that will never reach universal consensus. One example is abortion. Try to imagine the conversion of a prolife activist to a prochoice position by rational persuasion: each side is broadcasting on a different wavelength, so conversion is highly unlikely. For these reasons, neither force nor persuasive conversion is suitable for conflict resolution.

This leaves us with the third choice: negotiation by established procedures. The guiding principle for such a mechanism may be based on free choice or be based on mandate, such as mandatory arbitration. But the second of these introduces the use of force, and because this is fundamentally antirational, it is ethically unacceptable. The only rational, noncoercive mechanism for resolving ethical disputes is by negotiation between free agents in a political setting of liberty that allows respect for the autonomy of each.

This is the sense in which medical decision-making is, at its root, a collaborative effort between physician and patient, both searching for what is best for the patient's welfare [14]. It is useful in this regard to remember that the etymologic root for the word *doctor* is the Latin *docere*—to teach. The physician provides experience, scientific knowledge, and sensitivity to the patient's emotional state, whereas the patient provides the personal value system that forms the context in which decisions should be made.

Negotiation requires that all parties have sufficient information to make reasonable choices. This is the basis of the moral requirement for informed consent, which demands that patients be provided with adequate factual knowledge to understand the basis for medical recommendations in order to make rational decisions for their own care [15].

Patients are not alone in possessing autonomy. As I have argued elsewhere, physicians are also morally autonomous [12, 16], with their own value systems and their own senses of right and wrong. If a patient makes a choice or a demand regarding his or her own care that is so unreasonable or dangerous that the physician feels he or she cannot accept it, it is the physician's prerogative to withdraw, with proper notification, from the care of the patient. For example, a thoracic surgeon is not morally obligated to place on the transplant list a patient who is an inappropriate candidate, to replace an mitral prosthesis for the third time in a noncompliant, unrepentant intravenous drug user, or to give a prescription for more narcotic than is needed on the demand of a recent thoracotomy patient. In the case of surrogate decision-making for a child or incompetent patient, if a decision is made with a clearly malicious motive, the physician is bound not to withdraw, but to notify proper authorities for protection of the patient.

No generally accepted view of the good life has been provided either by the same divine revelation to all Americans or by a universally accepted rational description of goodness. Beneficence is a goal, therefore, that cannot be unilaterally achieved by a physician: the physician's values simply may not be congruent with those of the patient. In the words of the movie title: "Whose Life is it Anyway?". Beneficence, that is, doing what is good for the patient, cannot be the primary principle regarding medical decision making. Before it must come the other fundamental ethical principle, autonomy [17].

Application to the Case

How does all this apply to John Keating, the child whose case I just described? This child is terribly limited, even grotesque, with a markedly reduced lifespan and much higher than usual risk for any operation. It is easy to look at John, out of the context of family life, and decide that this life is clearly not worth living, and that the potential benefits to him are not worth the risks or expenditure of resources. It is also easy, out of the context of family life, to decide that no burden is too much for John or his family to bear to increase the number of his remaining days.

But the family sees the situation from a unique perspective. Their understanding of the life of their child—his own suffering as well as the stresses and losses they personally and their other children suffer because of his need for continuous and total care during whatever life remains to him—is different from the physician's.

The best ethical choice for Dr Mondavi is openly to disclose the important benefits and risks of no intervention, of a shunt procedure, or of a corrective operation, as best they can be discerned or estimated under these unusual circumstances, and allow the Keatings to make the choice.

That is what was done in this case. The Keatings asserted they wanted to do whatever was medically best for their son in the light of his disabilities, without regard to any burden for themselves. They chose a shunt, as the operation that offered him the greatest chance of immediate survival with reasonable relief of symptoms due to cyanosis and with the likelihood that it would last for the rest of what is expected to be his short remaining life.

The Rich Weave of Life

Another aspect of this case illustrates the richness of the fabric of life, which give both background and substance to ethical decision. During the discussion of the outcome probabilities of available treatments, Mrs Keating remarked, "We know John is not like other children, but we've never thought of him as anything other than our son, and we don't mind at all the extra things we have to do for him. The thing that bothers me more than anything else is when I have John out in his cart, and somebody comes up to us and, in a well-meaning way, sympathizes because John is so pitiable. I don't want sympathy, I don't want John to be pitied. He can't do much, but he thinks and he feels. He doesn't like for his little sister to play with him. Maybe she touches him too rough or something, but he screws up his face and cries when she starts to play with him.

"The thing that he really loves, though, is the feeling of a breeze on his face. If you wave a piece of paper in front of his face or blow on him gently, he breaks out into a grin, and sometimes just laughs out loud. He don't need pity."

It was clear after that discussion that this child was fully integrated into the life of the Keating family. Few physicians who heard that discussion with Mr and Mrs Keating would conclude that John's was a life not worth living. The medical-surgical conference did not have access to that information, so it might be argued that they did not have enough information to make the best decision.

But what if the Keatings had not been so eloquent in describing their son's place in their family? What if that particular value had remained hidden because of the family's inability to articulate it or because they chose to keep it private? Should that have made a difference in Dr Mondavi's decision to disclose *all* the benefits and risks and allow the family to make the choice, even though it might be one with which he did not agree? Not at all, in my opinion, because the choice is rightfully theirs whether they disclose all the reasons for it or not. Autonomy, which Mr and Mrs Keating were exercising on behalf of their son, John, does not comprise the right to make only the medically correct choice. It is the right to make the choice, even if that choice seems medically wrong [18].

An additional pertinent point is that it is not required for the physician to thrust decisions onto patients who are not prepared or are unwilling to make them. It is within the realm of control of self for a patient to delegate a decision to a religious adviser, family member, or physician [19]. We all have had the experience of hearing patients tell us that they do not know what to do, and ask what we would do, or even ask us outright to make the decision for them. We should not shrink from answering this question forthrightly and honestly [20].

Beneficence, Loyalty, and Cost Control

> No man can serve two masters: for either he will hate the one, and love the other, or else he will hold to the one and despise the other.
>
> Matthew 6:24

A second area in which pressure against good ethical practice has been building in recent years is that of cost control, and the gradual shifting of the burden for achieving it onto physicians. In the cardiac conference in which John Keating's case was discussed, the argument was made that the marginal gains to be achieved in his case, in view of his short life expectancy, could not justify the expenditure of tens of thousands of dollars for an operative hospitalization. We hear the argument more and more often that the decisions physicians make are responsible for most of our national health care expenditures. It is therefore up to physicians, it is said, to make medical decisions based on cost considerations.

I will argue that this is a morally dangerous and ethically unacceptable position, for it calls upon the physician to act as a double agent: advocate for the patient's best interest and protector of public monies. For us, as a profession, it remains true that we cannot serve two masters.

There is little question that health care resources must be protected, and no one should have a blank check on someone else's bank account. It is reasonable that decisions be made on limiting expensive diagnostic examinations and treatments under specified circumstances. I propose, however, that such decisions should not be made by a physician while caring for an individual patient.

Ethical problems related to divided loyalties are widespread in medicine. Military physicians [21], psychiatrists working in medical schools [22], and occupational physicians working for corporations [23] are called upon regularly to serve as physician to the soldier/student/worker, and at the same time to serve the interests of the institution that employs them. Adolescent physicians have divided loyalties to the patient and to her parents when their value systems collide [24]. Team physicians have responsibilities to the players as patients, but also to the team, and the interests of the two sometimes conflict.

And now, all physicians are being pressured into subverting their primary loyalty to their patients as they are cast in the role of protectors of the public purse and other health care resources [25]. Yet, the role of gatekeeper for purposes of cost control is ethically unacceptable for a physician [26] for at least two reasons: the patient is deceived and the patient is harmed by weakening of the physician-patient bond.

Deception is a form of dishonesty, so is usually morally reprehensible. The moral status of deception, however, is related at least in part to expectations [27]. For example, in the seventh game of the World Series last week, Minnesota used a decoy play to deceive Lonnie Smith into slowing down on the basepath, preventing his scoring. It was a costly deception: the Braves lost the World Series because of it. The deception was not immoral, however, because it was not only expected, but also had been mutually agreed to as acceptable, under the rules of baseball. Expectation does not excuse a deceitful action if deceit has not been agreed to: a politician who is expected to lie to us, and then does, is nevertheless morally culpable.

The expectation of patients is that physicians will be loyal to the patient's best interests. As physicians, we say that this is true, and the primacy of serving our patient's best interests is explicit in our codes of ethics [28] and has been from the time of Hippocrates: "Whatever houses I may visit, I will come for the benefit of the sick" [29]. It is morally permissible for us to act in another person's or group's best interest against that of our patient only if we explicitly tell the patient what we are doing, and he or she agrees.

Preserving trust of patients in the physician's loyalty is important for another reason: the nature of the healing relationship and the therapeutic value of trust. Once trust is lost, it is unlikely to recover, thus damaging the patient's future relationships with physicians and undermining this important component of healing.

Therefore, because the patient believes that we are acting in his or her best interest, and we have fostered that belief both as a profession and as individual physicians, it is simply wrong for a physician to place cost control above doing what is best for the patient. It violates the principle of beneficence and the corollary principle of loyalty to the patient's best interest.

This is not to say, however, that the physicians should not think about cost control. The high cost of medical care is a daunting problem that is now altering the nature of the health care system and the shape of the physician-patient relationship. Physicians, individually and as a profession, should be vigorously involved in addressing issues of cost control at the local, regional, and national levels. As advocates for our patients, it is morally incumbent upon us to do this. Our concern with cost control, however, should be at the policy-making level, not in the context of medical decisions for individual patients. The one exception is when two medical choices are of equal benefit, cost may become a valid consideration for the physician [30].

I am also not arguing that every conceivable technology should be used and every expenditure should be made for every marginal gain for every patient. Each diagnostic and therapeutic procedure we do has a small but definite risk, as well as costs to the patient not only of money, but also of time, energy, and usually additional suffering. Clearly, using expensive technology for every marginal gain is not morally required. What *is* required is that the physician's cast of mind when making small and large decisions for an individual patient be bent primarily toward the patient's best interest, wherever that interest lies.

Furthermore, I do not claim that cost should play no role in medical decision-making. Health care is only one of many demands on a patient's resources, and each of us should be free to choose whether, for example, to buy an expensive, wide-coverage health insurance policy or an inexpensive no-frills policy in order to spend the difference on other goods or services. But those decisions belong to the patient, not to the physician.

Novel Ethical Quandaries

> . . . The real high technology of medicine . . . comes as the result of genuine understanding of disease mechanisms, and when it becomes available, it is relatively inexpensive, relatively simple, and relatively easy to deliver.
>
> Lewis Thomas [31]

We have been considering relations between bioethics and our profession, our patients, and health policy. I would like to change gears for a moment and look to the future, specifically, to examine astonishing new technologies and the implications they have for bioethics.

It seems clear that new technologies may create ethical dilemmas. It is less widely understood that they may also solve ethical problems. For example, the development of the iron lung prevented many deaths due to polio in the 1940s and 1950s. Yet, the limited number of available respirators, particularly during polio epidemics, created a now-familiar ethical dilemma: by what criteria could one choose one of many afflicted individuals to place on the only available ventilator? Who should make those decisions? Who should pay for the expensive nursing care required? Problems of this sort could be answered in part by building large numbers of more efficient ventilators to keep more victims alive at great cost. This is investing in what Lewis Thomas called halfway technology [31]. Real high technology later wiped away those ethical problems, virtually at a single stroke: the development of vaccines that have nearly eliminated the disease itself. We now no longer need any respirators for treating polio; the ethical problems associated with polio have disappeared.

In our own area, diseases of the chest, a host of new technologies for treating atherosclerotic coronary artery disease have been developed and will continue to undergo further refinement. These include intravascular lasers to open blocked blood vessels by destroying atheromatous plaques, devices to cut, grind, shave, and pulverize atherosclerotic material, and intravascular stents to hold vessels open [32]. Pediatric cardiologists have developed techniques of therapeutic catheterization, including umbrellas to close a patent ductus arteriosus, clam shells to close atrial and ventricular septal defects, coils to occlude unwanted shunts and collateral blood vessels, and balloons, knives, and stents to open narrow flow pathways of arteries, valves, and veins [33]. These technologies are expensive and are not without risk to patients. Yet some hold the promise of treating cardiac problems more safely than with surgical approaches, and some may work where surgery cannot be used at all.

For cardiothoracic physicians, these devices are the new high technology. In reality, though, they are only halfway technologies and provide incomplete correction of disease processes. The true high technology of the 1990s and the next few decades lies in molecular biology and genetic engineering.

In the next few years and decades, biotechnology will produce revolutionary treatments of diseases beyond contemporary imagination, and these technologies will bring with them ethical dilemmas that are said to be qualitatively different from those we face now [34]. Developments in genetic engineering have raised questions of whether our technical skills have outstripped our moral responsibility, whether our ability to engineer our own genetic structure constitutes unwarranted, dangerous interference with nature, whether the eugenic movements formerly associated with totalitarian governments are about to reappear, and whether we are in danger of using our technology to transmute ourselves into something else, perhaps not even human [35]. It is worth asking whether our old ethics may still be useful in this brave new world.

Mapping the human genome is a $15 billion project that is already underway. Genetic markers have been found for many disorders, including cystic fibrosis, hemophilia, and muscular dystrophy. So-called contingency genes, which may denote vulnerability, are now known for hundreds of disorders, including Alzheimer's disease, manic-depressive syndrome, and familial hypercholesterolemia. As mapping of the genome continues, we will learn the location and structure of genes for personal characteristics, like eye color, body build, and probably intelligence and memory.

But reading the genetic code is only the beginning.

Genes can be manipulated with chemicals and drugs that can turn genes on and off to make them function more or function less, and with techniques to delete parts of chromosomes and to insert genes into cells. Genetic engineering is a reality. Two months ago, no less than 5 new experiments in human genetic engineering were approved by the Human Gene Therapy Subcommittee of the National Institutes of Health.

The possibilities, however, go far beyond disease prevention and treatment. It may be possible, by manipulating genes and their products, to change normal physiology for medical benefit; for example, to change histocompatibility characteristics of organs for transplantation. The drugs we now use to protect transplanted organs are blades with two edges—rejection on the one side and infection on the other—and avoiding injury by either edge is an important source of the large costs associated with organ transplantation. High costs and limited availability of donors have created a number of ethical problems: By what criteria can one choose one of many afflicted individuals to receive the only available donor organ? Who should make those decisions? Is it moral to increase the number of available organs by assuming that everyone has consented to donation at the time of death [36]? Who should pay for the expensive drugs and nursing care required for these patients? This is another example of an expensive, dilemma-generating halfway technology [31].

When it becomes practical to genetically alter an organ to be unrecognizable as foreign, no immunosuppression will be needed, and a heart transplant will be no more expensive than, say, closing an atrial septal defect. Furthermore, the organ probably will last indefinitely. In addition, there is no reason why the transplanted organ could not come from a cow or a pig, making an unlimited supply of fresh organs easily available.

Notice that this single technological advance, what Thomas called real high technology [31], will wipe away most of the difficult ethical issues associated with transplantation: there will be no waiting lists, no need to choose among indications for priority, no need to choose between living and cadaver donors of paired organs, and costs will be low. Furthermore, indications for transplantation will broaden markedly. For example, it will not be necessary to do coronary bypass grafting in patients with poor ventricular function, because the patient could simply receive a new heart, which would be cheap, easily available, and safe.

Of course, it is unlikely we will be doing coronary bypass grafting at all, because genetic engineering will probably make atherosclerosis a medical curiosity. An initial step will be underway soon: one of the programs approved this August by the Subcommittee on Human Gene Therapy will attempt genetic engineering of autogenous liver cells to treat familial hypercholesterolemia [37], in an effort to prevent its cardiovascular complications.

Another example of high technology reducing ethical dilemmas is the case of John Keating. By early detection, perhaps as early as the gamete, or by genetic engineering, congenital deformities like his will be prevented or changed, so no child will have to face life with the disadvantages John has, and all our technology to alleviate such malformations will not be needed.

The ethical challenges in genetic engineering, however, will not come from treating or preventing diseases, but from enhancing normal characteristics or manipulating the genes of germ-line cells [34, 38]. It is likely that mental functioning has a genetic basis. When it becomes possible to insert genes that will increase memory capacity or analytic speed by several magnitudes, how can we decide who should have such genes? Should they be purchasable by anyone who can afford them? Are there certain classes of people who alone should have access to such genetic manipulation, like the mentally retarded? Ultimately, are we in danger of producing progeny who are no longer recognizably human?

Genetic analysis shows that your daughter will be less than 3 feet tall when fully grown? We can remove that disadvantage by changing her genes so that she will be 5 feet 5 inches tall. But what about your son who will be of average height, 5 feet 10 inches? He would like to be more than 7 feet and be able to play professional basketball? No problem with that, is there? Or is there a moral difference between changing the body dimensions of your dwarf daughter and those of your normal son?

You don't want to be bald with a fringe of black hair like your father and grandfathers before you? No problem, a full crop of blonde, brown, black, or red hair is yours for the asking. To what extent should enhancing normal genes be permitted? Are there substantial moral differences between the cosmetic surgery of today and the genetic enhancement of tomorrow? What are the differences, and how should these ethical considerations affect public policy on genetic engineering?

Another area of apparent novelty in ethical challenge involves the gamete. Changing somatic cells is one thing, but when the genes of a sperm or an ovum are changed, the effects are seen not only in the treated individual, but in his or her every future descendant from that moment on. Instant mutations could be available to anyone. Should they be?

How Novel Are These Ethical Problems?

I suggest that the principles of bioethics, only a few of which we have had time to touch on this morning, can be applied to these new situations. Many issues appear radically different from problems we are used to dealing with but, at their core, are driven by the same ethical considerations as we use to think about contemporary dilemmas.

For example, W. French Anderson of the National Institutes of Health has argued that genetic engineering for germ-line changes and for enhancement should not be permitted, as a matter of policy, because "human values that our society considers important for the dignity of man would be significantly threatened" [38, 39]. One such threat, he says, is that the risks of such procedures may exceed the benefits.

Yet current bioethics, properly understood and followed, requires that we learn what it is possible to do, then learn what is safe, to avoid doing harm. Each gene can be thought of as a point in a Seurat painting or as a note in a Mozart symphony. Neither can be understood outside its relation to all the other parts of the work, and changing that iota changes the meaning and function of the overall design.

Consideration of the morality of gene manipulation must begin not only with an appreciation of the benefits to be gained, but also by understanding the harm that may be done as the effects of a single change reverberate throughout the genome and the whole organism. Once the risks and benefits are reasonably well understood, which is likely to take a very long time, then the choices of the conditions under which they should be used can be made in the context of the balances and tensions between autonomy and beneficence we have already discussed. Anderson's argument for a policy prohibiting genetic enhancement and germ-line engineering is correct in one regard: we do not know enough to be considering such gene therapy at this time. But there is no philosophic basis, in my opinion, for ruling out these possibilities for all time.

The Role of Physicians

As physicians, we should prepare ourselves to play a major, perhaps central role in the public debate over issues of health policy. We have unique experiences in caring for the sick and dying that lead us to understand, perhaps better than anyone, that life is uncertain and death is inescapable. Because of professional experiences, physicians have a sensitivity and wisdom about the human condition that will be invaluable in policy debates on limitations of use of resources [40]. At the same time, we should help to nurture a political environment that highly values liberty, as this is the setting in which truly ethical health care can flourish, allowing respect for the autonomy of both the patient and the physician.

Public debates between many interest groups, including physicians, make it clear that we think we have difficult ethical dilemmas now, but this brief review should indicate that much more difficult questions lie ahead. As physicians, we may most effectively be able to address these new issues by striving to understand the philosophic basis of bioethics. Such understanding will place our contributions to policy discussions on a higher plane of wisdom, and also will help us to to preserve the essence of the medical enterprise against sometimes well-meaning but destructive demands generated by social, political, and economic pressures.

Most importantly, we must pass on our appreciation of our uniquely medical ethic to the next generation of students and house officers. We can do this through our example of maintaining personally the highest ethical standards, through discussions with our colleagues, residents, and students, and through formal teaching in our medical schools and postgraduate programs.

While we involve ourselves in policy and education, however, we must not forget who we are and why we are here. We exist because people, like John Keating, become ill. When it comes to taking care of an individual patient, we have to keep clearly in mind the principles that arise from the nature of our healing profession. In the care of the sick, we must commit ourselves to serving a single master, which is the search for the truth of what is medically best for *this* patient lying on the sickbed in front of us. And ultimately, we must respect *his* vision of where his own good lies, as he, like each of us, steps to the beat of his own different drummer.

The penultimate draft of this work was reviewed by several colleagues. I am particularly indebted to Douglas B. Rasmussen, PhD, for his astute observations and suggestions, and gratefully acknowledge the helpful comments provided by Carolyn E. Reed, MD, and Corinne V. Sade.

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The Changing Unnatural History of Valvular Regurgitation

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Introduction of Dr Carabello by President Robert M. Sade

One of the real privileges of being President of the Association is the opportunity to invite a guest lecturer to speak at our annual meeting. It is a pleasure for me to introduce to you today Dr Blase Carabello, one of my cardiology friends and colleagues.

Blase is a native Pennsylvanian and earned his MD degree from Temple University. He served his residency in medicine at the Massachusetts General Hospital and completed his cardiology fellowship at the Peter Bent Brigham Hospital. He subsequently remained on the faculty at the Brigham and Harvard before moving on to the University of Virginia and subsequently back to Temple University, where he was Associate Professor of both Medicine and Physiology. Since 1985, he has been Professor of Medicine at the Medical University of South Carolina in Charleston.

Blase is one of those rare physicians who has distinguished himself in all three areas of academic medicine: he is an outstanding clinician, a first-class researcher, and a superb teacher. His major areas of research interest have been in ventricular function, cardiac hypertrophy, coronary blood flow, and valvular heart disease, all of great importance and interest to the cardiac surgeon. He has been the principal investigator in many research projects in these areas over the last several years, including several National Institutes of Health grants. He has served on the editorial boards of several journals, including the Journal of the American College of Cardiology. *Blase has been invited to speak at many scientific meetings, both nationally and internationally.*

He has had an equally distinguished career as a teacher. He has received in the past few years no fewer than 11 different teaching awards, mostly from students, including several Excellence in Teaching and Golden Apple Awards. His accomplishments as a clinician, his expertise as a leading edge researcher in cardiac function, and his superb skills in teaching made him an obvious choice for presenting the guest lecture at this annual meeting. It gives me great pleasure to present to you Dr Blase Carabello.

In the past 15 years three major advancements have improved the lot of our patients with left-sided valvular regurgitation. First, the concept that mitral and aortic regurgitation were similar volume overloading lesions has changed. Mitral regurgitation constitutes a nearly pure volume overload wherein the excess volume is ejected against relatively low pressure into the left atrium. On the other hand, aortic regurgitation represents a combined pressure and volume overload in which the excess volume being pumped is ejected against the relatively high pressure of the aorta. These differences in loading between mitral and aortic regurgitation produce a different response to operation. Afterload reduction after correction of aortic regurgitation increases ejection performance if it was decreased preoperatively. Conversely, afterload increases after mitral valve replacement, decreasing ejection performance. These differences make the left ventricle in mitral regurgitation less tolerant of preoperative dysfunction than the left ventricle in aortic regurgitation. Second, with respect to aortic regurgitation, reproducible indexes have been developed that identify when left ventricular dysfunction is present, leading to earlier operation in an attempt to avoid permanent ventricular dysfunction. In turn, earlier operation has led to a fall in operative mortality rate and an almost universal increase in left ventricular function if it was depressed preoperatively. Third, with regard to mitral regurgitation, recognition of the importance of the mitral valve apparatus in maintaining left ventricular function has led to an increased emphasis on chordal preservation during mitral valve operations. Early indicators suggest that these techniques will lead to improved postoperative left ventricular function, reduced operative mortality, and enhanced long-term survivorship for patients with mitral regurgitation. Thus, a change in concept regarding the pathophysiology of these lesions, a change in referral for patients with aortic regurgitation, and a change in operation for patients with mitral regurgitation have led to a favorable alteration in the unnatural history of left-sided valvular regurgitation.

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In the past two decades, a striking improvement has occurred in the outcome of patients treated surgically for valvular heart disease. A change in our concept of these diseases, a change in the characteristics of patients referred for aortic valve operation, and a change in the operation for mitral regurgitation are three of many reasons for the improved outcome.

A Change in Concept

Initially both mitral and aortic regurgitation were classified together as volume overloading lesions with obvious justification. In each lesion valvular incompetence allows only a portion of total left ventricular stroke volume to be ejected forward. Thus, in both lesions the ventricle must pump extra total volume to achieve a normal forward stroke volume. However, several major differences exist between these two left ventricular regurgitant lesions. In mitral regurgitation the excess volume is ejected against relatively low pressure into the left atrium. Therefore the excess work performed by the left ventricle is nearly entirely volume work; mitral regurgitation constitutes a nearly pure volume overload. In aortic regurgitation, the excess volume that the left ventricle pumps is pumped against the relatively high pressure of the aorta. Thus, the overload in aortic regurgitation constitutes a combined volume and pressure overload. The differences between mitral and aortic regurgitation were illustrated by Wisenbaugh and associates [1]. In their study, patients with aortic and mitral regurgitation were matched according to the amount of regurgitation present. As shown in Figure 1, end-diastolic stress, an indicator of preload, was increased above that of normal subjects in both groups of patients with regurgitation as would be expected in volume overload. However, peak systolic stress and end-systolic stress, indicators of afterload, were greatly increased in aortic but not mitral regurgitation. These data emphasize that afterload mismatch often constitutes a major part of the pathophysiology of aortic regurgitation. In fact, afterload in aortic regurgitation (a volume overloading lesion) may be increased to a level similar to that found in aortic stenosis, the prototypical pressure overload lesion [2]. Conversely, in mitral regurgitation, afterload mismatch is distinctly unusual except in extreme cases where left ventricular ejection performance is depressed [3].

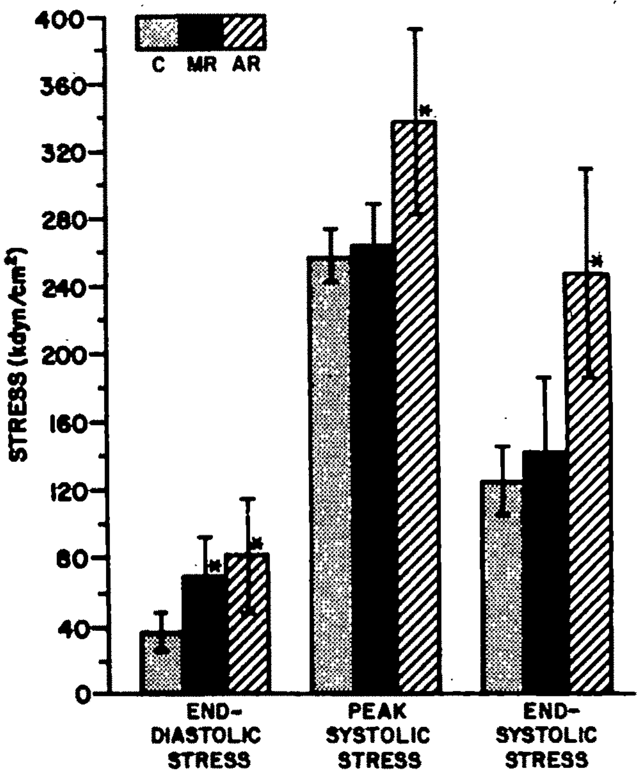

Fig 1. End-diastolic stress, peak systolic stress, and end-systolic stress are demonstrated for normal control subjects (C), patients with mitral regurgitation (MR), and patients with aortic regurgitation (AR). The two regurgitation groups were matched to have equal amounts of regurgitation. Preload as indicated by end-diastolic stress was increased similarly in both groups of regurgitation, but afterload as indicated by either measure of systolic stress was increased only in those patients with aortic regurgitation. (Reprinted from Wisenbaugh T, Spann JF, Carabello BA. Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation. J Am Coll Cardiol 1984;3:916–23, with permission.)

Not surprisingly, the different types of overload in aortic versus mitral regurgitation produce two different ventricular compensatory responses. The presence of both pressure and volume overload in aortic regurgitation leads to an approximately equal increase in left ventricular radius and wall thickness. However, in mitral regurgitation, the pure volume overload leads to a large increase in radius with little increase in wall thickness [4, 5]. As shown in Figure 2, the resultant amount of hypertrophy in mitral regurgitation is substantially less than that found in aortic regurgitation [6]. Thus, in mitral regurgitation there is less ventricular mass than in aortic regurgitation to perform the added workload [6, 7]. These differing patterns of hypertrophy and different loading conditions position the ventricles in these two diseases for a differing response to operation. In aortic regurgitation, ejection fraction typically increases after aortic valve replacement if ejection fraction was depressed preoperatively [8–10]. Conversely, ejection fraction almost universally falls after mitral valve replacement [9, 11, 12], although ejection fraction may be preserved when mitral regurgitation is corrected by mitral valve repair [13] instead of valve replacement. These differing responses are primarily predicated upon differences in afterload, which are in turn influenced by ventricular geometry. Afterload can be quantified by the LaPlace relationship where wall stress equals $p \cdot r/2h$ (p = ventricular pressure, r = radius, and h = thickness).

The changes in stress preoperatively and postoperatively for aortic and mitral regurgitation are demonstrated in Table 1. In aortic regurgitation, wall stress is elevated preoperatively primarily because systolic pressure is increased. After operation, systolic pressure is reduced, in turn reducing stress, resulting in a reduction in ventricular size and an increase in ejection fraction [8, 14] (Fig 3).

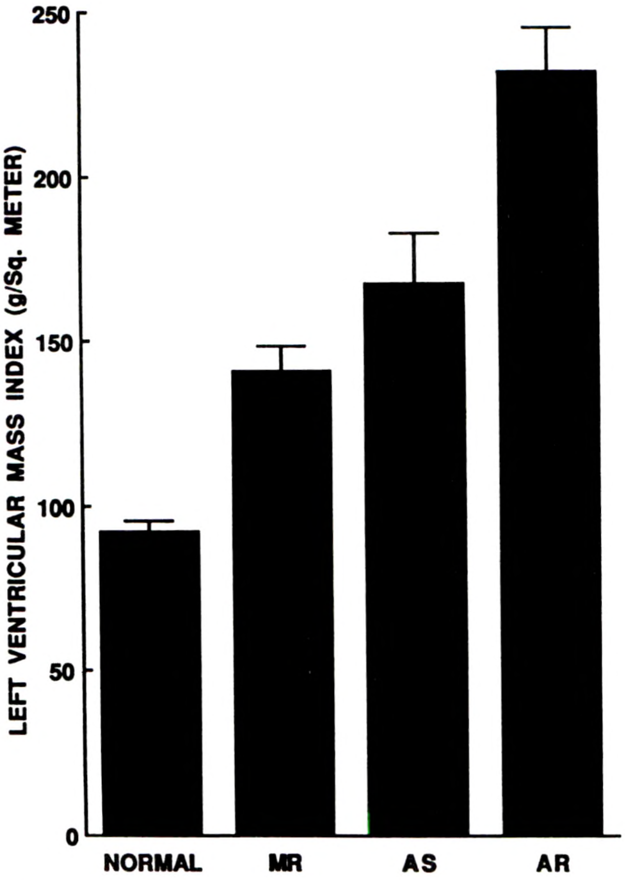

Fig 2. Left ventricular mass index is demonstrated for normal subjects, patients with mitral regurgitation (MR), patients with aortic stenosis (AS), and patients with aortic regurgitation (AR). Patients with mitral regurgitation have less extensive hypertrophy than those with aortic regurgitation. (Data obtained from Dodge HT, Kennedy JW, Petersen JL. Quantitative angiocardiographic methods in the evaluation of valvular heart disease. Prog Cardiovasc Dis 1973;16:1–23, by permission.)

In mitral regurgitation a lower than normal systolic pressure allows for normal wall stress despite the increase in the radius to thickness ratio [1]. However, after mitral valve replacement, systolic pressure increases. If the chordae tendineae have been severed, the ratio of radius to thickness remains elevated, which, together with increased systolic pressure, produces an increase in afterload with a resultant decrease in ejection performance [12]. The postoperative increase in afterload is greatly lessened when the chordae tendineae are preserved during either mitral valve replacement or mitral valve repair [15, 16]. Thus, in aortic regurgitation, if ejection fraction is depressed preoperatively it usually improves postoperatively because previously increased afterload falls. However, in mitral regurgitation, changes in loading produce at best a maintenance or possibly a worsening of ejection performance after operation because preload is reduced and afterload often increases.

Table 1. Mechanics of Valvular Regurgitation

Variable	AR Preop	AVR	MR Preop	MVR	MVRe
Ps	↑ ↑	nl	↓	nl	nl
r/h	nl	nl	↑ ↑	↑ ↑	nl
σs	↑ ↑	nl	nl	↑ ↑	nl
σd	↑ ↑	nl	↑ ↑ ↑	↑	nl
EF	nl or ↓	nl	nl or ↑	↓	nl

AR = aortic regurgitation; AVR = aortic valve replacement; EF = ejection fraction; MR = mitral regurgitation; MVR = mitral valve replacement; MVRe = mitral valve repair; nl = normal; Ps = peak systolic pressure; r/h = left ventricular ratio of radius to thickness; σd = diastolic wall stress; σs = systolic wall stress.

The differing left ventricular mechanics of the two types of valvular regurgitation produce different tolerances for the amount of left ventricular contractile dysfunction from which successful postoperative recovery can occur. Predictably, because operation for aortic regurgitation affords the ventricle improved loading postoperatively, somewhat worse preoperative left ventricular function can still produce a satisfactory result. On the other hand, unfavorable postoperative loading conditions and the relative lack of hypertrophy in mitral regurgitation permit less preoperative ventricular dysfunction to be tolerated. Table 2 shows current guidelines for the limits of indexes of left ventricular dysfunction that indicate a good versus a poor result [9–11, 14, 17–20]; they demonstrate that the left ventricle in aortic regurgitation can be substantially larger and have poorer ejection performance than the left ventricle in mitral regurgitation before a poor surgical result is anticipated.

Aortic Regurgitation: A Change in Time of Referral for Operation

Figure 4 demonstrates the results of aortic valve replacement in 1,479 patients of whom 29% had pure aortic regurgitation. There was a significant reduction in operative mortality for patients with aortic regurgitation in the years 1974 through 1981 compared with that of years 1967 through 1973 [21]. This trend is still continuing. Improved surgical techniques and the introduction of cold hyperkalemic myocardial protection helped reduce operative mortality during this time period. However, improved operative mortality and long-term survival for patients with aortic regurgitation are also due to a change in the patients being referred and a change in the condition of the left ventricle at the time of referral. Figure 5 demonstrates that there was a significant increase in the proportion of patients with aortic regurgitation in New York Heart Association class I and class II and a significant decrease in patients in class III and class IV being referred for operation from the earlier period to the later period in the study discussed above [21]. This trend has been almost universal. For instance, in 1973 the majority of the patients (84%) referred for operation at one center were in New York Heart Association class III or class IV [22] (Table 3). Today, very few patients are referred for operation in class IV [23]. Instead, most patients are currently in class II or class III at the time of aortic valve replacement.

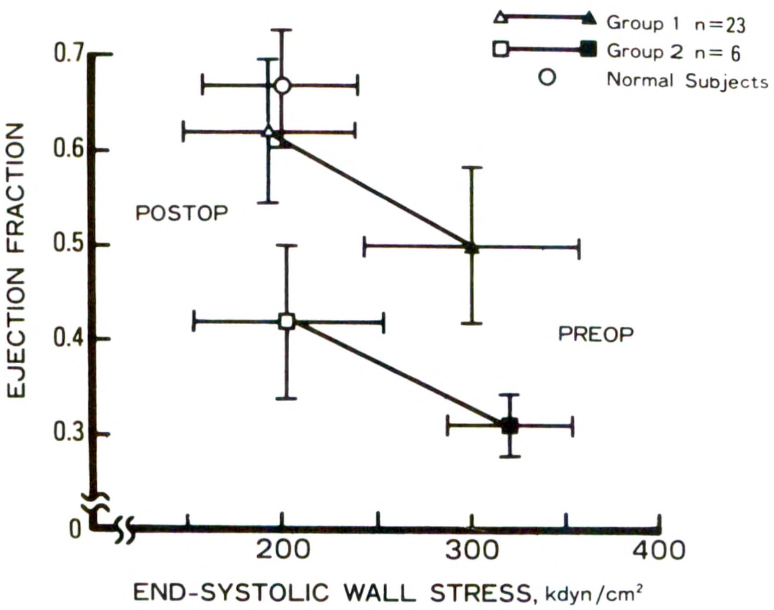

Fig 3. Ejection fraction and systolic wall stress in patients with aortic regurgitation are shown preoperatively (PREOP) and postoperatively (POSTOP). Group 1 consisted of patients with mild left ventricular dysfunction, whereas group 2 comprised patients with more severe dysfunction. In both groups, postoperative reduction in afterload (stress) allowed an increase in ejection fraction. (Reprinted from Taniguchi K, Nakano S, Hirose H, et al. Preoperative left ventricular function: minimal requirement for successful late results of valve replacement for aortic regurgitation. J Am Coll Cardiol 1987;10:510–8, with permission.)

This shift toward earlier referral has almost surely been influenced by the large number of reproducible studies that demonstrate reliable predictors of outcome for this disease. Thus, the referring physician now has guidelines upon which to base referral. These guidelines are in part predicated on left ventricular contractile function. Although contractile function is easily defined as the ability of the myocardium to generate force, clinical assessment of contractile function has been difficult. Ejection phase indices such as ejection fraction help measure contractile function but unfortunately are also affected by preload and afterload. Preload and afterload are in turn greatly altered in valvular regurgitation. Because of the dependency of ejection fraction on loading conditions, end-systolic dimension and volume, which are at least independent of preload [24], have been widely investigated in aortic regurgitation in an effort to circumvent the preload abnormalities present in that disease [1]. Echocardiographic end-systolic dimension or angiographic end-systolic volume used as adjuncts to resting ejection fraction or shortening fraction appear to be the best predictors of outcome for aortic regurgitation (see Table 2). Thus, in one study (Fig 6), patients with an end-systolic dimension greater than 55 mm had only a 40% 3½-year survivorship after aortic valve replacement, whereas patients with an end-systolic dimension of less than 55 mm had a 90% 3½-year survivorship [25]. A remarkable number of studies have confirmed this end-systolic dimension or its angiographic equivalent (approximately 100 mL/m^2) as an important easily obtainable diagnostic "breakpoint" between a good outcome and a poor outcome [9, 14, 26, 27].

Another study from the National Institutes of Health group demonstrated that even if left ventricular dysfunction had developed, it could be reversed if aortic valve replacement was performed within 14 months of detection of the dysfunction [28] (Fig 7). Improved function after operation is due to a reduction in afterload and probably improvement in muscle function [8, 29]. Currently, the majority of patients with left ventricular dysfunction have a substantial improvement after operation, a striking change from a decade ago when only 50% of patients demonstrated such an improvement [30] (Fig 8).

Today, a typical patient with aortic regurgitation is followed up closely by his or her physician with a careful history, physical examination, and an echocardiogram. Once symptoms appear or echocardiography demonstrates that left ventricular dysfunction is beginning to develop, the patient is usually referred for aortic valve

Table 2. Indicators of Poor Surgical Outcome

Regurgitation	EDV (mL/m^2)	ESVI (mL/m^2)	ESD (mm)	EF
AR	>220 [14, 17]	>110 [9,14]	>55–60 [10, 19]	<0.45 [10]
MR	>160 [17, 18]	>60 [9,17]	>45 [20]	<0.60 [11]

AR = aortic regurgitation; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic dimension; ESVI = end-systolic volume index; MR = mitral regurgitation.

Modified from Carabello B. On the differences between mitral and aortic regurgitation. J Invasive Cardiol 1989;1:125–8, with permission.

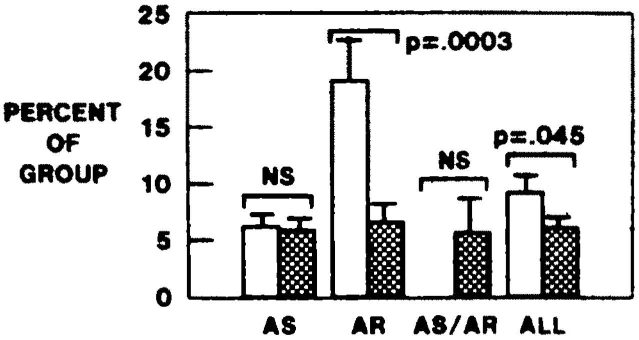

Fig 4. Operative mortality for patients with aortic stenosis (AS), aortic regurgitation (AR), and mixed disease (AS/AR) is demonstrated. Open bars *indicate early experience from 1967 to 1973, whereas the* cross-hatched *bars demonstrate later experience from 1974 to 1981. Operative mortality for aortic regurgitation dropped dramatically from the earlier to the later time period. (Adapted from Scott WC, Miller DC, Haverich A, et al. Determinants of operative mortality for patients undergoing aortic valve replacement. Discriminant analysis of 1,479 operations. J Thorac Cardiovasc Surg 1985;89:400–13, with permission.)*

Table 3. Cardiothoracic Ratio Related to Preoperative New York Heart Association Classification

Cardiothoracic Ratio	No. of Patients	Preop NYHA Classification		
		II	III	IV
≤0.50	58	16 (28%)	33 (56%)	9 (16%)
>0.50	114	11 (9%)	66 (58%)	37 (33%)

NYHA = New York Heart Association.

Taken from Isom OW, Dembrow JM, Glassman E, Posternack BS, Sackler JP, Spencer FC. Factors influencing long-term survival after isolated aortic valve replacement. Circulation 1974;50(Suppl 2):154–62, with permission.

replacement. This has resulted in patients being referred when they are less symptomatically impaired and have better left ventricular function than they did 15 years ago. The outcome of earlier referral is a lower operative mortality and a striking improvement in left ventricular function if it was depressed preoperatively.

Mitral Regurgitation: A Change in Operation

Simple mitral valve replacement (with chordal excision) has the highest operative mortality and the poorest postoperative outcome of all left-sided valvular lesions [21, 31, 32]. As with aortic regurgitation, several investigators have searched over the past decade for markers of ventricular function that would be prognostic of outcome. As demonstrated in Table 2, many such predictors have been developed, yet adherence to these predictors has failed to lower the operative mortality for mitral regurgitation in the same manner that occurred for aortic regurgitation. At least one reason for the persistently worse outcome in mitral regurgitation (even in the absence of coronary disease) relates to the mitral valve apparatus and its destruction during mitral valve replacement [13, 33–37]. Attention has been refocused on previous reports indicating that the mitral valve apparatus is much more than a passive structure existing only to prevent prolapse and leakage of the mitral valve. The attachments of the mitral valve to the papillary muscles cause a left ventricular shape change in early isovolumic systole as the papillary muscles pull the chordae tendineae taut, shortening the long axis and lengthening the short axis. The early systolic increase in minor axis length produced by the mitral valve apparatus utilizes the Frank-Starling mechanism, which prepares the minor axis for enhanced shortening later in systole. Thus, the mitral valve apparatus contributes substantially to overall left ventricular systolic function. Its destruction (Fig 9) produces a significant fall in ven-

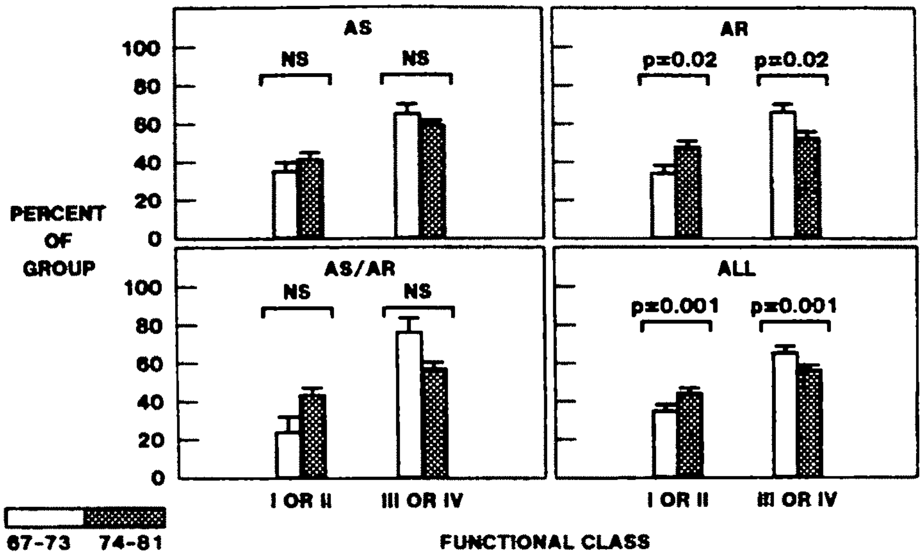

Fig 5. New York Heart Association functional classes for patients with aortic valve disease are demonstrated. In the upper right hand corner it is apparent that patients with aortic regurgitation (AR) in functional class I or II increased from the earlier referral period to the later one, whereas patients in functional class III or IV decreased. (AS = aortic stenosis; NS *= not significant.) (Reprinted from Scott WC, Miller DC, Haverich A, et al. Determinants of operative mortality for patients undergoing aortic valve replacement. Discriminant analysis of 1,479 operations. J Thorac Cardiovasc Surg 1985;89:400–13, with permission.)*

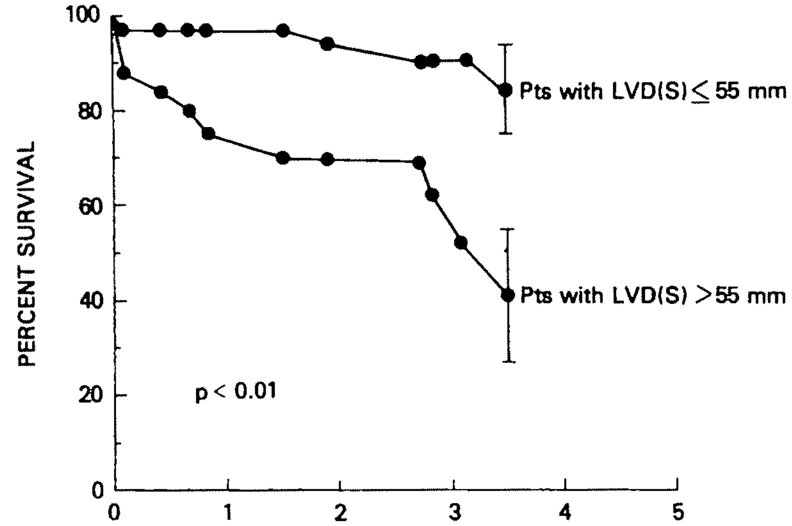

Fig 6. The influence of left ventricular end-systolic dimension [LVD(S)] on survivorship in patients with aortic regurgitation is demonstrated. (Reprinted from Bonow RO, Rosing DR, Kent KM, Epstein SE. Timing of operation for chronic aortic regurgitation. Am J Cardiol 1982;50:325–36, with permission.)

tricular performance [35] and can do so even if overall ventricular function was preserved before operation. Thus, even if clinical indexes demonstrate preserved preoperative ventricular function, operation can cause dysfunction, making functional indexes for mitral regurgitation less predictive than those for aortic regurgitation.

Nearly all previous studies examining ejection performance after mitral valve replacement for mitral regurgitation found a significant fall in ejection fraction postoperatively [9, 11–13]. Initially, this fall was explained by the unfavorable change in loading conditions that occurs when mitral competence is restored: afterload increases

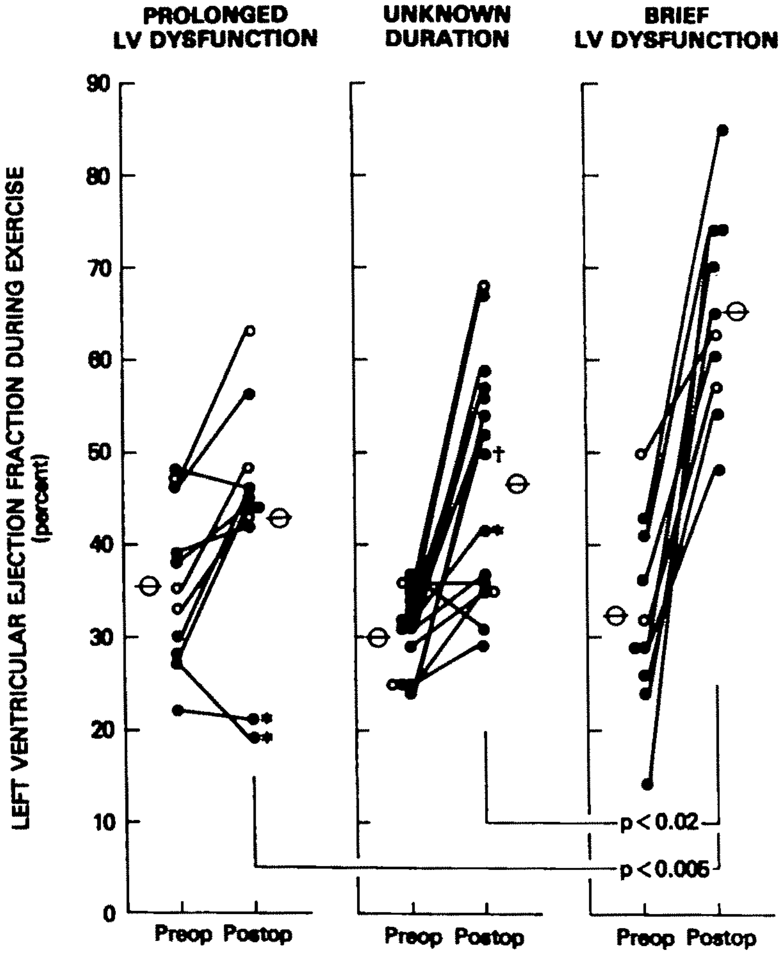

Fig 7. Preoperative and postoperative left ventricular (LV) ejection fraction during exercise is demonstrated for patients with aortic regurgitation who had prolonged left ventricular dysfunction, dysfunction for an unknown duration, and dysfunction for a brief period of time. Those patients with a brief period of dysfunction improved dramatically after aortic valve replacement. (Reprinted from Bonow RO, Rosing DR, Maron BJ, et al. Reversal of left ventricular dysfunction after aortic valve replacement for chronic aortic regurgitation: influence of duration of preoperative left ventricular dysfunction. Circulation 1984;70:570–9, with permission.)

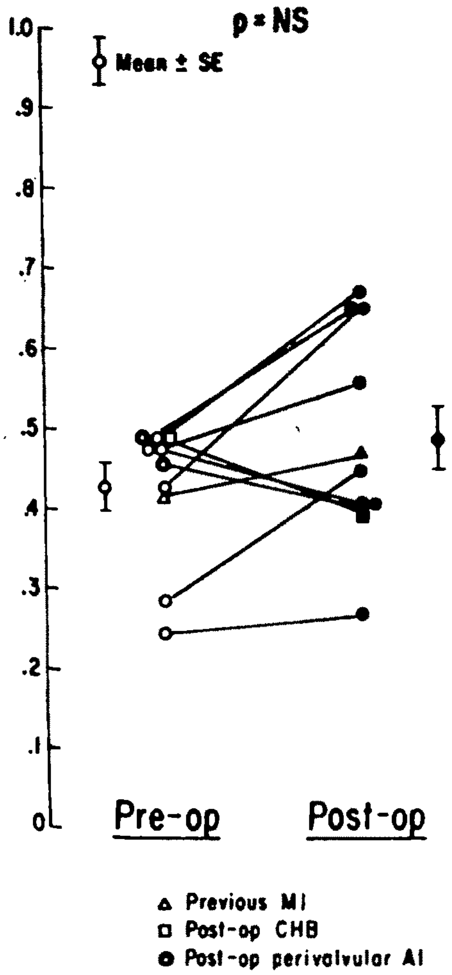

Fig 8. Ejection fraction is shown for 10 patients with aortic insufficiency and preoperative left ventricular dysfunction operated on between 1973 and 1977. Postoperative ejection fraction (Post-op, *14.5 months after operation) did not significantly improve from the preoperative* (Pre-op) *value.* (AI = *aortic insufficiency;* CHB = *complete heart block;* MI = *myocardial infarction;* NS = *not significant.) (Reprinted from Clark DG, McAnulty JH, Rahimtoola SH. Valve replacement in aortic insufficiency with left ventricular dysfunction. Circulation 1980;61:411–21, with permission.)*

Table 4. Comparison of Operative Mortality Rate[a]

	Repair		Replacement	
Reference	n	Percent Mortality	n	Percent Mortality
Oury et al [39]	34	0	46	13
Duran et al [40]	255	1.8	307	11.4
Yacoub et al [41]	86	5.0	46	11.0
Oliveira et al [42]	84	4.9	101	5.0
Adebo and Ross [43]	21	0	44	6.8
Total	480	1.9	544	10.3

[a] $p < 0.0001$ for the comparison between the repair and replacement groups.

Modified from Cosgrove DM, Chavez AM, Lytle BW, et al. Results of mitral valve reconstruction. Circulation 1986;74(Suppl 1):82–7, with permission.

(as the low impedance pathway is closed off) and preload is reduced. Both changes would reduce ejection fraction, and logically the observed fall in ejection fraction was ascribed to these changes. However, recent studies examining ejection performance after procedures that conserved the mitral apparatus demonstrate that ejection performance is preserved rather than decreased [13, 15, 16]. However, in these conservative procedures, mitral valve competence is also restored, which should have produced exactly the same adverse loading conditions as with pure mitral valve replacement. Thus, some other mechanism besides loading changes is needed to explain how ejection fraction is preserved after operation involving chordal preservation. One explanation is that preservation of the mitral valve apparatus preserves ventricular ejection performance by preserving contractile function (see Fig 9). Preserved function in turn counteracts the increase in afterload, helping to maintain ventricular systolic shortening. A second explanation is that chordal preservation allows a reduction in heart size, helping to reduce the postoperative radius/thickness ratio, in turn decreasing stress (afterload) despite closure of the left

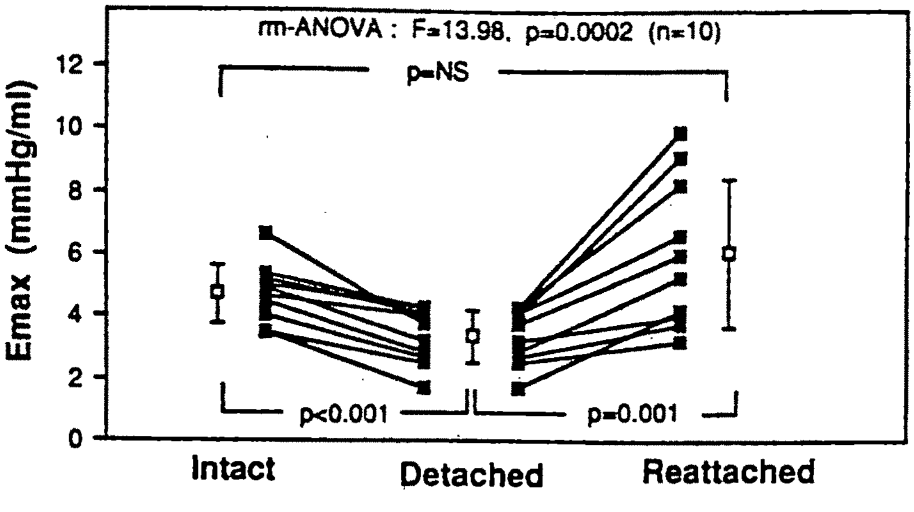

Fig 9. Ventricular elastance (E_{max}), *an indicator of left ventricular contractile performance, is demonstrated in a canine ventricle with chordae tendineae intact, after chordal detachment, and after chordal reattachment. Ventricular performance falls substantially after detachment of the chords and is restored after reattachment.* (NS = *not significant.) (Reprinted from Sarris GE, Cahill PD, Hansen DE, Derby GC, Miller DC. Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of valvular-ventricular interaction. J Thorac Cardiovasc Surg 1988; 95:969–79, with permission.)*

atrial pathway for ejection [16]. Regardless of the mechanism, preservation of left ventricular function together with reduced incidence of endocarditis, valve failure, and thromboembolic phenomena all act in concert to yield reduced operative and late mortality after mitral valve repair versus mitral valve replacement [38–43] (Table 4).

Conclusion

In the past decade we have learned that aortic and mitral regurgitation are two quite different diseases which respond quite differently to valve replacement. Earlier referral for aortic valve replacement for aortic regurgitation before the onset of left ventricular dysfunction has led to improved operative and long-term results for this disease. In the coming decade, recent emphasis on the importance of the mitral valve apparatus together with the achievement of the technical skills allowing its preservation will almost surely provide improved results for the correction of mitral regurgitation as well. Thus, a combination of improved understanding, earlier referral, and enhanced surgical techniques have allowed us to positively change the unnatural history of left-sided valvular regurgitation.

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Selective Surgical Approach for Atrioventricular Reentrant Tachycardia

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From September 1986 through September 1990, 60 operations were performed in 55 patients (32 male and 23 female; age, 1 to 76 years) for ablation of accessory pathways of atrioventricular reentrant tachycardia; 6 patients had additional cardiac procedures. Between September 1986 and August 1988 the initial surgical approach was exclusively epicardial with adjuvant cryoablation (EPI) in 23 patients (group 1) for a left free wall (LFW) pathway in 11, right free wall (RFW) in 3, posteroseptal (PS) in 7, and anteroseptal in 2. During September 1988 through September 1990, 32 patients (group 2) had the initial surgical approach tailored to the location of the mapped accessory pathway: endocardial approach (ENDO) for LFW in 17 and for juxtanodal pathway in 2, EPI for RFW in 3 and for PS in 9, and combined ENDO and EPI for AS in 1. There was no early or late death in either group. In group 1, 2 patients with LFW pathway had development of recurrent preexcitation in the same compartment requiring ENDO reoperation 10 and 11 months later, 1 with anteroseptal pathway needed immediate ENDO and EPI reoperation, and another with LFW, who required pericardial patch repair of a left atrial tear, had a thromboembolic stroke 2 days later. No serious complications occurred in group 2, but 2 patients with PS required reoperation before discharge for a second accessory pathway in another compartment (1 RFW and 1 LFW). Additionally, 4 patients (2 in each group) had from the beginning ablation of two pathways in different compartments. On complete late follow-up (mean, 28 months) all patients are back to preoperative levels of activity and are free of preexcitation. Our experience indicates that with a selective approach in atrioventricular reentrant tachycardia, based on the location of the pathway and the possibilities and limitations of each technique, LFW pathways are more reproducibly ablated with the ENDO technique, whereas the EPI approach is easier for PS and RFW pathways with equally excellent results.

(Ann Thorac Surg 1992;53:200–6)

The first successful surgical interruption of an accessory pathway in atrioventricular reentrant tachycardia (AVRT) (the Wolff-Parkinson-White syndrome) was reported in 1968 by Cobb and associates [1]. Since then, the surgical treatment of supraventricular tachycardia associated with this conduction abnormality has evolved with improved methods for identification and interruption of these accessory pathways. At the present time, there are two major surgical approaches to the abnormal pathway. The classic technique, developed initially by Sealy and associates [2, 3] and separately by Iwa and associates [4], and more recently refined by Cox and co-workers [5], approaches the pathway from the inside of the appropriate atrium and consists of an incision of the endocardium to dissect the atrioventricular (AV) groove, thus interrupting the ventricular insertion of the pathway. Subsequently, Guiraudon and colleagues [6, 7] developed a surgical approach that does not require the opening of the atrial cavities; the AV groove is dissected from the outside of the heart by an incision of the epicardium at the atrial level, and the AV fat pad and vessels are reflected onto the ventricular aspect to provide access to the valve annulus. Adjuvant cryotherapy is applied to the AV junction to destroy any conducting fiber that might remain intact.

Excellent results have been reported by the proponents of each of these two methods, although each approach has advantages and disadvantages. Our own experience began in September 1986, using exclusively the epicardial approach for the first 2 years. The approach was modified after that, particularly in patients with left free wall pathways. The purpose of this report is to evaluate the initial experience of the same surgeon with the division of accessory AV pathways in an attempt to evaluate the efficacy and indications of each approach in patients with AVRTs and accessory pathways in different locations.

Material and Methods

Patients

From September 1986 to September 1990, 55 patients underwent 60 operative procedures for surgical ablation of accessory AV pathways of AVRT, also known as Wolff-Parkinson-White syndrome. There were 32 male and 23 female patients, aged 1 to 76 years (mean, 32 years). All operations were performed by the same sur-

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Table 1. Results of Operation for Atrioventricular Reentrant Tachycardia

Variable Location of Primary AP	Exclusively Epicardial (9/86–8/88)				Selective (9/88–9/90)				
	LFW	RFW	PS	AS	LFW(endo)	RFW(epi)	PS(epi)	JN(endo)	AS (epi & endo)
No. of patients	11	3	7	2	17	3	9	2	1
Second AP at initial operation	1	. . .	1	. . .	2	. . .	. . .	. . .	. . .
Additional cardiac procedure	1	. . .	1	. . .	2	1	1	. . .	. . .
Reoperation									
Early	. . .	. . .	. . .	1[a]	. . .	. . .	2[b]	. . .	. . .
Late	2[c]	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .

[a] Reoperation at 2 days with endo and epi technique. [b] Reoperation at 2 days in each, for a second RFW AP in 1 and LFW AP in the other. [c] Reoperation with endo approach for recurrent preexcitation in same compartment, at 10 and 11 months.

AP = accessory pathway; AS = anterior septal; endo = endocardial approach; epi = epicardial approach; JN = juxtanodal; LFW = left free wall; PS = posterior septal; RFW = right free wall.

geon (A.S.G.) at University Hospitals of Cleveland. Six patients had additional cardiac procedures, consisting of coronary artery bypass grafting in 5 and closure of an atrial septal defect in 1. Four patients had a secondary accessory pathway identified and ablated at their initial operation, after ablation of the primary pathway.

Surgical Technique

The heart was approached through a median sternotomy, and quadripolar plaques were fixed on the left atrium and ventricle for electrical stimulation and to serve as reference electrodes.

Intraoperative electrophysiologic mapping was done epicardially during normal sinus rhythm, atrial pacing, ventricular pacing, and reciprocating supraventricular tachycardia without cardiopulmonary bypass. In the first 29 operations, sequential bipolar recordings with a handheld probe were used. In the next 31 procedures, a multiple-point computerized mapping system with a band bearing 24 pairs of electrodes and wrapped around the base of the heart was used [8].

EXCLUSIVELY EPICARDIAL APPROACH. During the first two years of the study, all pathways were ablated exclusively through an epicardial approach in (group 1; n = 23). Table 1 details the location of the primary pathways in these patients. The AV fat pad was incised epicardially near its junction with the atrial wall and dissected down toward the ventricle, exposing the shoulder of the ventricle and going down to the AV valve ring. The fat pad was encircled with heavy silk suture to allow exposure and mobilization and to protect the coronary vessels from freezing, as described by Guiraudon and associates [9]. This dissection was performed without cardiopulmonary bypass in all patients who had right free wall, paraseptal, or anteroseptal pathways. In the 11 patients with left free wall pathway, the dissection was carried out after establishment of normothermic cardiopulmonary bypass with a two-stage venous cannula and a membrane oxygenator.

After reflection of the AV fat pad toward the ventricle and dissection of the AV connections down to the valve annulus, a series of overlapping cryolesions were carried out to cover completely the exposed valve annulus in the dissected compartment. This was achieved by applying a liquid nitrogen cryoprobe cooled to a temperature less than −70°C for 2 minutes on the AV groove and the adjacent ventricular myocardium and atrial wall to ensure complete and permanent ablation.

Posteroseptal pathways were approached by making an epicardial incision at the junction of the AV fat pad with the right atrium and then extending the incision to the left side of the heart, dividing the middle cardiac vein, and reflecting the coronary sinus toward the atrium. The fat pad containing the coronary arteries was dissected away from the atrial and ventricular surfaces, and the incision was extended through the right atrial–left ventricular sulcus to expose the posterosuperior process of the left ventricle and the adjacent portion of the left free wall. During application of the cryolesions in the posteroseptal region, antegrade conduction was continuously monitored by measurement of the PR interval, and the cryoprobe was removed if AV block occurred.

In the 11 patients with left free wall pathways, the dissection and cryosurgery were done with cardiopulmonary bypass on the normothermic beating heart except in 3 patients (27%) in whom the heart was electrically fibrillated when a tear developed near the base of the left atrial appendage. The tear was small in 2 patients and could be closed primarily with pledgeted sutures. In the third patient, the tear occurred at the junction of the ice ball of the cryolesion with the rest of the thinned out left atrial wall, which was beating back and forth next to the rigidly frozen cryolesion. The tear measured about 1.5 × 1 cm and required closure with a patch of pericardium sutured to the annulus of the mitral valve and to the edges of the torn left atrium with continuous Prolene (Ethicon, Somerville, NJ) sutures, taking care to orient the mesothelial surface of the pericardium toward the cavity of the atrium.

Additional coronary revascularization procedures were performed in 2 patients in this group after completion of the surgical dissection and cryoablation and electrical testing for interruption of the pathway. In 2 patients, a second accessory pathway was demonstrated and was dissected in another compartment with the same methods.

SELECTIVE APPROACH. During the last 2 years of the study, between September 1988 and September 1990, a more selective surgical approach was used in another 32 patients (group 2). The location of the primary pathway and the approach selected for each are detailed in Table 1. In patients with left free wall pathways, cardiopulmonary bypass was instituted after completion of the mapping, using two venous cannulas and a membrane oxygenator. Systemic hypothermia at 28°C and cold blood potassium cardioplegic arrest were used. A left atriotomy was carried out parallel to, and about a centimeter to the left of, the atrial septum. An endocardial incision was made about 4 mm upstream from the AV valve ring, extending from trigone to trigone, as described by Cox and associates [5]. The dissection of the AV fat pad was extended to the epicardial reflection on its ventricular aspect. After this dissection, the two ends of the supraannular incision were squared off to preclude any juxtaannular pathways from surviving the dissection. No adjunct cryolesion was applied for the left free wall pathways.

Two patients in group 2 had juxtanodal pathways (AV node reentry) and underwent cryosurgical ablation without surgical dissection by application of small cryolesions, using an ophthalmic cryoprobe, around the periphery of the AV node, as described by Cox and co-workers [10], using an endocardial approach through the cavity of the right atrium. Another patient in group 2 with an anteroseptal pathway was approached with a combined epicardial and endocardial method, mapping the bundle of His under direct vision through a right atriotomy and applying a cryolesion on the epicardial side while continuously monitoring AV conduction. Three patients with right free wall pathways and 9 with posteroseptal pathways in group 2 underwent operation with the epicardial approach (see Table 1). Two patients with left free wall pathways in this group were found to have another pathway in the posteroseptal space at electrophysiologic evaluation after ablation of the primary accessory pathway, and these pathways were ablated at the same operation through an epicardial approach. Four patients in group 2 underwent additional procedures: closure of an atrial septal defect in 1 with a right free wall pathway, and coronary artery bypass grafting in the other 3 (see Table 1).

In all patients, electrophysiological testing was carried out at the end of the operation, then pairs of temporary epicardial pacemaker wires were left in the walls of the right and left atria, in the anteroseptal part of the right atrium near the aortic root, and in the right and left ventricles for postoperative electrophysiological testing. These electrodes were used for daily bedside electrophysiological testing using rate incremental pacing until the development of second-degree AV block. In addition, with the help of these wire electrodes, all patients underwent, before discharge, detailed electrophysiological studies using multichannel recorders and other equipment available in the electrophysiological laboratory, and care was taken to ensure that abnormal conduction was not present in either retrograde or antegrade fashion. These predischarge studies could be carried out without intravascular catheterization and were similar to the preoperative studies, but without the need for endocardial mapping.

Results

The overall results are summarized in Table 1. There were no early or late deaths in either group. Complete follow-up was available by direct contact with the patients or their physicians. The duration of follow-up ranged from 5 to 53 months with a mean of 28 months.

Exclusively Epicardial Approach

One patient in group 1 with an anteroseptal pathway was found on the first postoperative day to have recurrent preexcitation. He underwent reoperation the next day, and repeat intraoperative mapping confirmed the recurrence in the anteroseptal space. It was attributed to primary failure to divide the accessory pathway, which was mapped and which was probably obtunded after the first operation, resulting in a negative electrophysiological test at the end of the procedure. Reoperation was carried out by a combined endocardial and epicardial approach as described for group 2. The patient had no further evidence of preexcitation after that, but returned to the hospital about 4 weeks later with a clinical picture of pericardial constriction and underwent a third procedure to dissect away the pericardium, which had become somewhat thickened and intimately adherent to the heart, particularly over the right atrium. This patient had no further complications after that. In another patient with left free wall pathway, who had the large tear in the left atrial wall during cryosurgery requiring repair with a pericardial patch, sudden left-sided hemiparesis developed on the second postoperative day. Computed tomographic scanning showed evidence of a right cerebral infarct, and echocardiographic study showed probable clot in the area of the patch. The patient was anticoagulated with warfarin sodium (Coumadin) and gradually recovered function on the left side with clearing of his neurological deficit. In another 2 patients with left free wall pathways who had a negative detailed electrophysiological study before discharge from the hospital, recurrent AVRT developed several months after the initial operation. Both underwent reoperation, and at repeat mapping they were found to have accessory pathways in the left free wall compartment, one only functioning in a retrograde direction. Reoperation was carried out using the endocardial approach as described in the Material and Methods section, at 10 months and 11 months postoperatively, with no further recurrence of arrhythmias.

Selective Approach

Two of the patients with posteroseptal pathways and negative electrophysiological testing at the end of the operation manifested evidence of preexcitation by bedside electrophysiological testing on the first postoperative day. In each instance a reoperation was carried out the next day, and repeat intraoperative mapping showed a second accessory pathway in the right free wall region in 1 patient and in the left free wall in the other. These second pathways were ablated at reoperation using the described selective approach with no further evidence of preexcitation.

The length of stay in the hospital after operation was 8.1 ± 1.1 days for patients with left free wall pathways who had an endocardial operation, 7.9 ± 1.0 days for those with left free wall pathway and an epicardial operation, and 7.1 ± 0.9 days for patients with posteroseptal and right free wall pathways who had an operation with the epicardial approach. The differences between these numbers were not statistically significant. However, the length of postoperative stay in the surgical intensive care unit was significantly longer ($p < 0.00$) for patients with the endocardial approach (51 ± 5 hours) than for those with the epicardial approach (26 ± 3 hours).

There were no early or late deaths in either group. There were no other postoperative complications or surgical morbidity besides those described in this section. Antiarrhythmic drugs were given to 1 patient in each group before their discharge from the hospital because of atrial flutter or fibrillation. Late follow-up revealed no recurrence of circus movement tachycardia. All patients have resumed their preoperative level of activity.

Comment

The rationale for operation for supraventricular tachycardias is based on comprehensive correlation between cardiac anatomy and electrophysiology. It necessitates close collaboration between the cardiac surgeon and the clinical electrophysiologist to ensure successful surgical management. Considerable understanding of these mechanisms in patients with the Wolff-Parkinson-White syndrome has evolved since Sealy first cured a patient with incessant tachycardia using electrophysiological surgery [1].

Atrioventricular reentrant tachycardias of the preexcitation syndrome require well-defined AV connections to bridge the atria and the ventricles at two distinct sites, namely the AV node–His bundle and the accessory AV pathway. In up to 15% of patients another one or more accessory AV pathways are found. Activation can reciprocate between the atria and ventricles in either direction, resulting in orthodromic or antidromic AV tachycardia [11]. In the juxtanodal variety of this tachycardia, the "accessory" pathway is an AV nodal one, which can be anatomically just outside the AV node.

The aim of operation in AVRT is to dissect widely and deeply the atrioventricular sulcus in the region of the accessory pathway. Two approaches are currently used, the endocardial approach pioneered separately by Sealy and associates [2] and by Iwa and co-workers [4], and perfected by Cox and colleagues [5], and the epicardial approach pioneered and perfected by Guiraudon and associates [7].

We started our surgical experience at Case Western Reserve University School of Medicine and University Hospitals of Cleveland in September 1986, using exclusively the epicardial approach in the first 2 years. Because of a perception of some difficulties with this approach in patients with left free wall pathways, we adopted a more selective approach in the next 2 years of the study. This report was designed to compare the two approaches in 55 consecutive patients. There were no operative deaths with either approach, but the complications and failures observed in the two groups warrant further attention and examination.

No serious complications of bleeding or myocardial infarction occurred in either group. This probably reflects care for secure hemostasis and care to protect the coronary vessels during accessory pathway section and ablation. Although it is theoretically possible that the epicardial technique manipulation of the normothermic beating heart may increase the risk of myocardial ischemia, we have not encountered any postoperative infarction.

Of the 5 patients in whom evidence of recurrent preexcitation or AVRT developed, 3 exhibited it early, on the first postoperative day. These were elicited by the use of bedside electrophysiological testing. The efficacy of this approach in daily evaluation of the surgical results in AVRT has been recently reported by Fisher and associates [12]. The method allows identification of these patients before a predischarge complete study, thus permitting prompt intervention early on. The patient in group 1 in whom an early recurrence developed after an epicardial approach to the anterior septal region by dissection in the right coronary fossa probably had persistence of the accessory pathway conduction and required a combined approach such as described by Guiraudon and co-workers [13]. After our experience with him, we have adopted this approach in those rare patients with an accessory pathway in this location. The other two early recurrences of preexcitation occurred in patients in group 2 who had an ablation of an accessory pathway in the posterior septal space at the initial operation. Intraoperative mapping with a hand-held probe had been carried out in both. At reoperation, a second accessory pathway in a different compartment was identified in each of them. These second pathways had not been identified at electrophysiologic testing at the end of the operation, and probably represent pathways that were transiently obtunded during the initial operative procedure and that were masked during the previous electrophysiologic study at cardiac catheterization.

The late recurrence of preexcitation or AVRT in 2 patients in group 1 with left free wall pathways, with a residual pathway still in the same compartment at late reoperation (10 and 11 months after the initial procedure), is due to accessory conduction in the region of the left fibrous trigone, near the left main coronary artery. This area is relatively difficult to dissect from the epicardial approach, especially when the fibers are in the subendocardial location. Although recurrence of preexcitation has been reported by other groups using the endocardial surgical approach [14, 15], we have not seen any in our 17 patients with left free wall pathways in group 2 where we carried out the dissection from trigone to trigone, as recommended by Cox and associates [5].

Although our study was not randomized between the epicardial and endocardial approaches to left free wall pathways, and the epicardial approach was used earlier in our experience, the complications and late recurrence of preexcitation and AVRT encountered by us with the use of the epicardial approach to these pathways prompted us to select the endocardial approach to them. The total lack of complications and late recurrence after endocardial section of the left free wall pathway in our group 2 patients is significantly different from the results observed in comparable patients in group 1. Interestingly, Guiraudon and associates [11] recently reported changing from the "en bloc" approach of epicardial dissection of the AV fat pad to a "direct" approach for left free wall pathways. Instead of incising the epicardium along the atrial limit of the fat pad and mobilizing the fat pad toward the ventricle, the "direct" approach exposes the AV annulus through an incision of the epicardium along the ventricular wall and proceeds to dissect any plane of cleavage over this wall until the AV annulus is identified. We have not used this "direct" approach modification of the epicardial method in view of the excellent results observed with the endocardial section.

Our observations are in agreement with those reported by Page and co-workers [16], that the epicardial approach is quite suitable for interrupting accessory AV pathways of the posterior septal and right free wall regions, whereas the endocardial approach with an incision from trigone to trigone and clean, meticulous dissection of the mitral valve annulus under cardioplegic arrest results in a more reliable interruption of left free wall pathways. The surgeon undertaking these procedures should be prepared to use either or both approaches depending on the electrophysiologic information obtained before and during operation.

Ablation of accessory pathways by percutaneous catheter application of radiofrequency current is gaining popularity [17–19], and the electrophysiologic surgeon may face more challenging situations when catheter ablation fails to interrupt the pathway or results in serious complications. Recognizing the advent of radiofrequency ablation and its success in eliminating AVRT and even AV nodal reentrant tachycardia, there are still patients in whom this technique will fail and patients who are coming to operation for other reasons. It is therefore important that these surgical techniques still be in the hands of surgeons who have the expertise to perform them. These operations will not be used as frequently as they were in the past, but there clearly are going to be cases where they will need to be not only remembered, but skillfully applied. These were difficult enough techniques for surgeons to learn well and apply with the success rates that we expect, and this is a skill that should not be lost. Although now most cases will come to radiofrequency ablation, and operation will be applied far less frequently, it will be no less needed, and the surgical skill required to deal with these cases should be available. The reservoir of expertise will still be necessary for the smaller volume of patients who will need operation.

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DISCUSSION

DR TAKASHI IWA (Kanazawa, Japan): I congratulate Dr Geha on his success in treatment of Wolff-Parkinson-White syndrome by a selection of epicardial and endocardial approaches. His selection of approaches for Wolff-Parkinson-White syndrome may be a solution to arguments regarding endocardial and epicardial approaches in operation of Wolff-Parkinson-White syndrome, although I have no intention to change my endocardial approach as we obtained almost 100% success by my original endocardial approach, which is different from those of Dr Sealy and Dr Cox.

In the most recent 160 consecutive patients with Wolff-Parkinson-White syndrome who were operated on, we had no deaths, no preexcitations, no recurrences, no tachycardia attacks, and no serious complications, although one of multiple accessory pathways remained in 2 patients without preexcitation or tachycardia attack, and AV block occurred in 1 patient after tricuspid valve replacement for associated Ebstein's anomaly, but not due to the ablation procedure.

I would like to ask Dr Geha one question. We operated on 38 cases of associated Ebstein's anomaly among 424 patients with Wolff-Parkinson-White syndrome or 93 patients with right posterior wall and septal accessory pathways. In other words, 39% of patients with right posterior wall and septal Wolff-Parkinson-White syndrome had associated Ebstein's anomaly that had to be operated on simultaneously. How many cases of associated Ebstein's anomaly did you have in your series, and how did you manage them?

DR GEHA: Thank you, Dr Iwa. I mentioned in the presentation that we had 3 patients who had Ebstein's anomaly. One had a pathway in the right free wall and 2 in the posterior septal compartment. So it is certainly a smaller incidence than you had encountered in your group. None of them had symptoms related to their Ebstein's anomaly that compelled an operation, and we therefore did not do anything surgically about the Ebstein's anomaly in those 3 patients.

DR GERARD M. GUIRAUDON (London, Ont, Canada): Dr Geha asked me to comment on this report. I am pleased to congratulate Dr Geha for his informative presentation. He seems to have taken the best of every current technique. He showed that the epicardial approach for a posterior septal pathway and right free wall is safe and effective, whereas the endocardial approach should be used for the left free wall. This may be true if the en bloc approach is used. This statement may be true when the en bloc dissection of the left free wall is used, although it may no longer stand true when a direct approach is used. The direct approach is carried out without mobilizing the fat pad and without the need for cardiopulmonary bypass, and has been free of complications for the first 100 patients.

DR GEHA: Thank you, Dr Guiraudon. It is mentioned in the manuscript, and I did not have time to discuss it in the oral presentation, that Dr Guiraudon did describe subsequently what he calls the "direct approach" to the epicardial technique for left free wall pathways. It entails separating the AV fat pad from the ventricular wall, going up to the AV valve ring. We have not used this approach in this series, so I have no experience with it.

DR JAMES L. COX (St. Louis, MO): I would also like to add my congratulations to Dr Geha and his group for providing us with some nonbiased and objective data. Dr Guiraudon and I have been carrying on a rather lively discussion about these various approaches for the last several years, and I think this really is the first series that I can recall in which the results have been directly compared with a single surgeon preforming the two procedures.

My first comment is that one of the supposed advantages of the epicardial technique proposed in the past relates to the fact that the heart is warm and beating during the dissection. Allegedly, by performing the operation with the heart beating, once the pathway is divided, if another pathway is present in another area, one is more likely to find it at the time of operation than if the procedure had been performed under cardioplegic arrest.

In Dr Geha's series, however, there were six such pathways, four of which were found at the time of operation. There were two in the epicardial group and two in the endocardial group. More importantly, there were two pathways that appeared several weeks or several days after operation, and interestingly, both of those occurred in the epicardial dissection group. Thus, the argument that the epicardial approach, because it is performed on the warm beating heart, allows one to detect other pathways that were not previously suspected is not consistent with Dr Geha's data.

Second, I had the advantage of seeing this manuscript several days ago, and I categorized the results in a little different way. If one looks at all those pathways that were approached by the two different techniques, there were 21 pathways approached by the endocardial technique, 18 primary and 3 as redo operations for failed epicardial approaches. Of those 21 pathways, all were divided, there were no complications in any of the patients, and there were no recurrences or reoperations. In other words, the results were perfect.

There were 37 pathways approached by the epicardial technique, 35 primary and 2 later reoperations. Of those 37 pathways, 11 were on the left free wall side, 3 of which had atrial tears (27%). There was a 6% recurrence rate, 2 reoperations, and 1 stroke in the epicardial group.

Those results are not terribly unlike the results that other surgeons have had with these two surgical procedures.

My first question is, do you think that there is any present rationale for using the epicardial approach for left free wall and anterior septal pathways? Those pathways comprise 56% of your patients and 65% of our patients. Second, as it presently takes about 15 minutes to perform a posterior septal dissection endocardially, I would be interested in knowing how long your posterior septal dissections by the epicardial technique take. Finally, did you have any instances of heart block in either the posterior septal or anterior septal dissections?

Again, I appreciate the invitation to discuss this paper, and congratulate Dr Geha on providing us with important objective data on the virtues of these two operative approaches in patients with the Wolff-Parkinson-White syndrome.

DR GEHA: Thank you, Dr Cox. It is true that there were 2 patients with the epicardial approach in the posterior septal compartment in whom evidence of another pathway developed on the first postoperative day. It turned out to be in the right compartment in 1 and in the left compartment in the other. Both were toward the paraseptal area, one on the right, one on the left, and we reoperated on them during that hospitalization. I would say there probably is some obtundation of these pathways with the freezing in the area adjacent to them. And I think your point is well taken that the fact that you do the operation epicardially does not necessarily rule out missing a pathway in another compartment, at least in our hands. Perhaps in Dr Guiraudon's hands the results may be different.

As to your other questions, I agree that right now, with our experience, we would do all left free wall pathways with an endocardial approach and the anterior septal pathways with a combined endocardial and epicardial approach, freezing from the inside and doing the dissection from the outside, monitoring for bundle of His recordings. I have not had any experience, as I mentioned, with the "direct approach" that Dr Guiraudon has recently advocated with the epicardial technique for left free wall pathways, and therefore I cannot compare that. So at this time I would approach that compartment endocardially, as described by Dr Cox.

Regarding the incidence of heart block, we have not seen any. We have monitored these patients carefully for conduction during the epicardial dissection. Of course, with an endocardial dissection, you cannot do that, but we are somewhat away from the AV node.

And as to the posterior septal epicardial dissection, it takes us about 30 minutes to carry out the dissection and cryoablation. The heart is beating and supporting the circulation, and its cavities are not entered. This probably is no longer than it would take to do the endocardial resection when you consider the time required to cannulate and institute cardiopulmonary bypass, then rewarm and wean the patient off bypass.

DR FRED H. EDWARDS (Washington, DC): Over the last 2½ years we have divided slightly more than 70 pathways and we have independently come to the same conclusion as you: the operative approach ought to be dictated by the location of the pathway. We do this type of operation exactly as you have described except for posteroseptal pathways, which we believe are optimally treated by endocardial cryoablation. The endocardial cryoablation is quite easy and it obviates the often tedious posteroseptal dissection associated with either the endocardial or epicardial approach. Generally speaking, from the time we open the right atrium until we have eliminated the posteroseptal tract with cryoablation is around 10 minutes. I have no questions for Dr Geha and his associates, but I would like to offer my comments as a fairly enthusiastic endorsement of their approach.

Calcification of Porcine Valves: A Successful New Method of Antimineralization

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Despite distinct advantages over mechanical cardiac valve prostheses, the use of bioprosthetic valves remains limited due to poor long-term durability, primarily as a result of tissue calcification. A novel anticalcification process, based on treatment of porcine bioprostheses with a derivative of oleic acid, has been developed by one of us (J.M.G.) (US Patent Number 4,976,733). This process employing 2-aminooleic acid (AOA) was tested in a juvenile sheep model. Terminal studies after a 20-week interval included hemodynamic, radiographic, morphologic, and quantitative tissue calcium analyses. All control valves (n = 4) had thickened, immobile, heavily calcified leaflets, whereas all AOA-treated valves (n = 8) were pliable and free of calcium deposits. Calculated valve orifice areas for controls (0.9 ± 0.2 cm^2) (mean ± standard error of the mean) was less than for AOA-treated valves (2.0 ± 0.3 cm^2) ($p < 0.05$). Radiographic calcification scores were greatly elevated in the control (25.5 ± 5.6) versus AOA-treated valves (0.5 ± 0.5) ($p < 0.002$). In quantitative mineralization studies, the mean calcium content of the control leaflets was 129 ± 21 milligrams per gram dry weight cusp tissue versus 7.7 ± 5.8 mg/g for AOA-treated valves ($p < 0.001$). Pathologic examination confirmed heavy calcification in the control leaflets, which was essentially absent in the AOA-treated leaflets. However, cuspal hematomas in areas of structural loosening and surface roughening were noted in AOA-treated valves. This anticalcification process dramatically reduced mineralization of porcine valve prostheses in this model.

(Ann Thorac Surg 1992;53:207–16)

About 40,000 patients undergo cardiac valve operations in the United States annually [1]. Despite advances in valvular reconstructive techniques, the majority of patients undergoing valve procedures receive prosthetic replacement [2]. Development of prosthetic devices has evolved mainly along two lines: mechanical and bioprosthetic. The advantage of superior durability for mechanical valves is offset by the requirement for patient anticoagulation to suppress thromboembolic problems. Conversely, bioprosthetic valve patients do not require indefinite anticoagulation, but the valves are prone to calcification and degenerative failure prompting reoperation. The ability to suppress this tissue mineralization could allow safer expansion of the benefits of bioprostheses to a wider patient population. Accordingly, a recently developed method of tissue anticalcification based on treatment with 2-aminooleic acid (AOA) [3] was tested using a standard porcine bioprosthetic valve in a juvenile sheep model previously demonstrated to mineralize tissue valves rapidly [4–6].

Material and Methods

Twelve juvenile sheep underwent successful mitral valve implantation with modification of a previously described technique [4–6]. These animals, 2 males and 10 females, were 14 to 24 weeks of age with a body mass range of 25 to 31.5 kg at the time of implantation. After an overnight fast the animals were given atropine (0.2 mg/kg) and acetylpromazine (0.55 mg/kg) intramuscularly followed by shearing of the operative and access sites. Parenteral prophylactic antimicrobial injections (cephapirin and penicillin G benzathine and procaine suspensions) were begun preoperatively and continued for 72 hours. The animals were then given general anesthesia with ketamine (22 mg/kg) followed by halothane inhalation and neuromuscular blockade with pancuronium (0.1 mg/kg). A large-bore rumen tube was passed orally for gastrointestinal decompression. The animals were placed in the right lateral decubitus position, the right femoral artery was cannulated for arterial inflow from the cardiopulmonary bypass circuit (Cobe VPCML, Lakewood, CO), and the left femoral artery was used for arterial pressure and blood gas monitoring. A left thoracotomy incision was used for cardiac exposure. Venous return was from retrograde cannulation of the right ventricle through the main pulmonary artery. Myocardial protection was afforded by antegrade cold, oxygenated, crystalloid cardioplegia and

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perfusion was carried out with moderate systemic hypothermia. The prosthetic mitral valves were placed in the supraannular position through a left atriotomy using interrupted atrially based pledgeted sutures. The mural leaflet and its chordal attachments were preserved. The animals were extubated within a few hours of operation and were ambulatory and taking food and water the evening of the operation. Parenteral analgesics were given for 48 hours postoperatively. The single left chest tube was intermittently aspirated and then removed 24 to 48 hours postoperatively. Therapeutic anticoagulation was not employed in any animal. Although thought to affect tissue calcification, there was no attempt to limit oral or intravenous calcium administration [7].

In addition to the 12 surviving animals there were two operative deaths. It was observed that these animals had coronary air emboli with postoperative ventricular dysfunction and arrhythmias leading to their deaths. In the right lateral decubitus position the left main coronary artery is superiorly oriented, and it readily and passively fills with air when the left heart is opened for valve insertion. A modification of the operative technique whereby the left main coronary artery was controlled with a Rumel tourniquet on a 3-0 polypropylene suture was instituted. This suture was passed around the left main coronary artery and the vessel was occluded during the aortic cross-clamp period. Occlusion began after cardioplegia delivery and continued until complete deairing of the cardiac chambers after removal of the cross-clamp. This maneuver appeared to have prevented coronary air emboli in the remainder of the experiments. These two operative deaths are not considered further.

Of the 12 implants, four were control valves, which were clinical quality 25-mm porcine bioprostheses (Medtronic Heart Valve Division, Irvine, CA). The experimental valves were prepared by treating the same type of valve with AOA in a newly developed process [3]. The animals were housed in a controlled indoor environment, were exercised daily, had access to feed and water ad libitum, and were under close veterinary medical supervision during the preoperative, convalescent, and chronic phases of the study. The sheep were given levamisole nematocidal treatment preoperatively and vaccinated against tetanus, *Clostridium perfringens* C and D, vibrio, pasteurella, and ovine ecthyma. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

After the 20-week implantation period the animals were anesthetized and instrumented through a median sternotomy for the hemodynamic studies. High-fidelity micromanometers (Millar Instruments, Houston, TX) were placed in the left atrium and left ventricle for continuous pressure measurements. Thermodilution cardiac outputs were obtained with balloon-tipped flow-directed pulmonary artery catheters (Edwards Swan-Ganz catheter; Baxter, Santa Ana, CA). The data were accumulated through an analog to digital conversion board (Data Translation, Inc, Marlborough, MA), sampled every 4 milliseconds, stored, and analyzed through a 386 microprocessor using an interactive program developed in this laboratory (James M. Bradford, PhD, copyright 1988–1991 Emory University). Valve orifice areas were calculated using the modified Gorlin formula for the mitral valve [8]:

$$\text{MVA} = \text{CO}/[(\text{HR})\ (\text{DFp}')\ (37.9)\ (\sqrt{\text{grad}})]$$

where MVA = mitral valve area, CO = cardiac output, HR = heart rate, DFp′ = diastolic filling period, 37.9 = empiric constant, and grad = mean mitral valve diastolic gradient.

After the hemodynamic studies the animals were killed with an injection of a commercial euthanasia solution (Beuthanasia-D; Schering Corporation, Kenilworth, NJ). The valves were excised, gross photographs were taken, and x-ray exposures of the valves were then made using a uniform mammographic technique. The sheep underwent a formal postmortem examination by a board-certified veterinary pathologist (Dirck Dillehy, DVM, PhD). A simple scoring system was employed to grade the radiographic appearance of the calcium deposits. The leaflet deposits were assigned scores based on the deposit size and number. A sum was then determined for each valve (see Appendix). The valves were placed in 4% formaldehyde.

After fixation, the aortic wall and cusps were removed from the stent. A radial section of each valve cusp and its adjacent aortic wall was processed for histologic examination.

The remainder of the leaflet segments were rinsed five times in distilled water, lyophilized overnight, weighed, and acid hydrolyzed under vacuum at 90°C with 2 mL of ultrapure redistilled 6 N HCl (GFS Chemicals). After 24 hours the samples were dried under vacuum and the residue resuspended in 1 mL of 0.3 N HCl then diluted with 0.01 N HCl. Quantitative calcium levels were then obtained using inductively coupled plasma analysis (Georgia Tech Research Institute, Atlanta, GA).

Specimens were embedded in JB-4 glycol methacrylate medium (Polysciences, Inc, Warrington, PA). Sections 2 to 3 μm thick were cut with glass knives and stained with hematoxylin and eosin, von Kossa's stain (for calcium phosphates), and the Movat pentachrome stain (for collagen, elastin, and mucopolysaccharides).

Statistical analyses were carried out on a microprocessor (Intel 386/24 megahertz, Santa Clara, CA) using proprietary software (RS1 release 4.2, BBN Software Products Corporation, Arlington, VA) with the advice of a statistician (Elmer Hall, PhD, Emory University, Atlanta, GA). Data are displayed as mean ± standard error of the mean. Comparison between AOA and control groups for valve orifice areas was made with a one-tailed unpaired t test. The radiographic scores followed a non-Gaussian distribution and Fisher's exact test was employed. Quantitative calcification scores were compared by two-tailed unpaired t tests. Significant differences were said to exist at the $p < 0.05$ level.

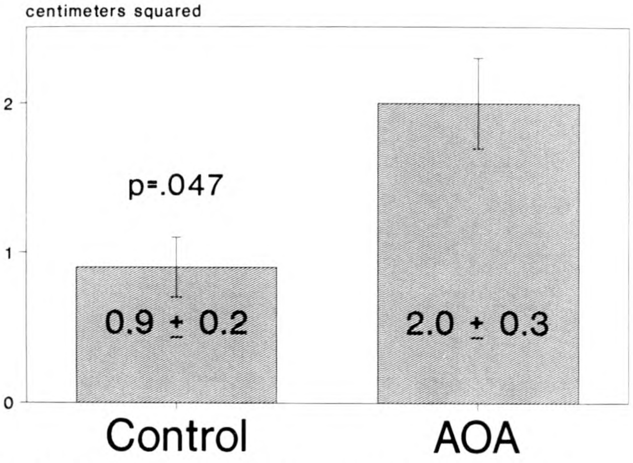

Fig 1. Mean valve orifice areas for control and 2-aminooleic acid–treated (AOA) valve implants (mean ± standard error of the mean).

Results

The sheep generally did well through the planned 20-week implant period. Four animals had an apparent perioperative peripheral nerve injury leading to a functional loss comparable with foot drop. Two injuries promptly resolved, and the two permanent losses were successfully treated by splinting of the extremity allowing satisfactory ambulation. One animal with a control valve implant had sudden development of signs of pulmonary congestion at 10 weeks after implantation and died within hours of onset. Hemodynamic studies were not done. Postmortem examination of that animal showed a tightly stenotic, heavily calcified valve with cardiac chamber and pulmonary findings compatible with severe mitral stenosis. Similar symptoms developed in 2 additional control valve animals, which underwent early elective terminal hemodynamic studies, one 13 and one 19 weeks after implantation. Only 1 of the AOA-treated valve animals did not reach the planned 20-week implant period. This animal had development of pneumonia and for humane reasons was put to death after hemodynamic study at 10 weeks. The mean increase in mass for the control valve sheep was 4.7 kg as compared with 16.4 kg for the AOA animals.

The animals with valves treated with AOA had larger calculated valve orifices than the untreated, control-valve sheep. The calculated valve areas are displayed in graphic form in Figure 1. Typical digitized waveforms collected from a control and from a treated valve implantation are shown in Figure 2.

Photographs representative of the gross appearance of the typical extensive calcification of the untreated valves and the freedom from calcium deposits of the AOA-treated valves are shown in Figure 3. As illustrated by the photographs, on gross examination the control valves were extensively mineralized with immobile leaflets and multiple calcific excrescences as seen with bioprosthetic valves explanted from patients after degenerative failure. The AOA-treated valves had pliable leaflets free of gross calcific deposits. However, focal cuspal hematomas and areas of cuspal thinning were noted in virtually all valves.

Light microscopic studies confirmed the difference in mineralization between AOA and untreated valves. However, in virtually all cases, AOA-treated valves had morphologic features suggesting generalized tissue degradation, including structural loosening, surface roughening, and deep cuspal collections of erythrocytes. Control, untreated valves had these features only rarely. Focal surface roughening was noted to be present on AOA-treated valves before implantation. Histologic features of treated and control valves are illustrated in Figure 4.

The mammographic exposures (Fig 5) demonstrate the marked contrast between the radiolucent AOA-protected valves and the heavily opacified calcium deposits on the control valves. The highly significantly different grouped radiographic scores are given in the bar graphs of Figure 6.

The leaflet quantitative calcification levels are highly significantly elevated in control valves compared with AOA-treated valves (Fig 7). By way of comparison, the quantitative calcium level for untreated, nonimplanted control valves ($n = 6$) was 0.6 ± 0.08 mg calcium/g dry tissue. Examination of individual AOA-treated valve quantitative calcium levels showed that six of the eight valves had levels so low that they were no different from the untreated, nonimplanted control valve levels.

The salient feature found at necropsy was universal pulmonary or systemic vascular congestion compatible with mitral stenosis in the control valve sheep. Atelectasis and pneumonia were found in some animals in both groups. No macroscopic intracardiac thrombi were noted in any animals. None of the valves were thought to have evidence of endocarditis, and the sewing rings were well endothelialized.

Comment

The optimal surgical treatment of cardiac valvular disease may be restoration of the native valve to a satisfactory functional state through conservative reparative procedures [9]. Unfortunately, the valvular pathology most often encountered at operation is irreparable due to advanced rheumatic, degenerative, ischemic, or calcific destruction necessitating prosthetic valve replacement. For more than two decades reliable mechanical and bioprosthetic alternatives for valve replacement have been available. Homograft valves remain an option, but use continues to be limited by supply, increased technical demands for implantation, and yet unproven advantage. For most patients the prosthetic valve choice is based on an individualized judgment weighing the durability and increased risk of thromboembolism for the mechanical valve versus freedom from chronic anticoagulation but increased risk for tissue degeneration and reoperation for the bioprosthetic valve. The choice is influenced by patient age and life expectancy, access to medical care, childbearing plans, contraindication to anticoagulation, lifestyle, assessment of medical compliance, cardiac rhythm, alterations of calcium metabolism, sizing and gradient considerations, position, and institutional or surgeon biases [10–15].

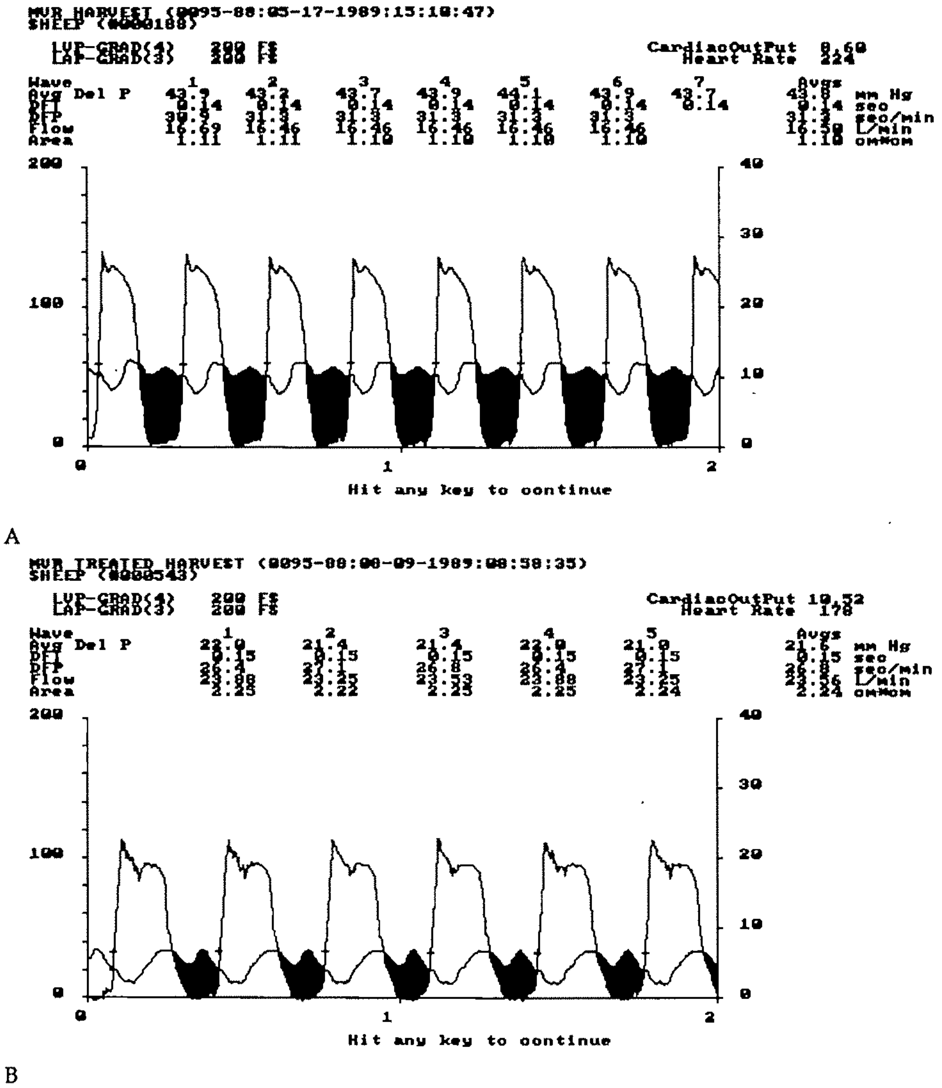

Fig 2. (A) Representative digitized left atrial and left ventricular waveforms used for determination of transvalvular gradients and valve orifice areas through customized software. Note the high mean gradient of 43.8 mm Hg for the control valve after volume loading to give a cardiac output of 8.6 L/min. (B) Representative waveforms for a treated valve after volume loading to give a cardiac output of 10.5 L/min.

The clinical problem of porcine tissue valve failure is illustrated by the valve survival data (freedom from reoperation or death) from Bolooki and associates [16] which are representative of other series. After pooling their data from Carpentier-Edwards and Hancock implants (no significant difference), 5-year valve survival approximates 84% to 91% of implants and falls to 70% to 75% at 8 years. Follow-up from other series at 14 to 15 years revealed a freedom from valve failure as low as 31% to 41% [17, 18].

It is well established that the leading cause of clinical bioprosthetic valve failure is primary tissue degeneration, which occurs in 60% to 75% of cases [13, 19]. The most common clinical cause (approximately 85% [19]) of this degeneration is related to valve tissue calcification. As bioprostheses otherwise function well as valve replacement devices, the importance of the search for methods of attenuating the mineralization of these valves is evident.

The pathogenesis of bioprosthetic calcification is incompletely understood but does not appear to be completely explained by a single mechanism. There are certainly factors that are host related, as well as those specific to the bioprosthesis itself. The physical forces to which the valve tissue is exposed [20, 21], recipient mineral metabolism [22], and host environment at the valve locus [1] may all play a role in facilitating calcification. It is clear that mechanical stress plays a role in promotion of calcification and is thus an active area of research and development efforts. However, it does not appear that mechanical deformation is necessary for mineralization to proceed [1, 13, 23, 24]. Exposure to the extracellular ions associated with the host mineral metabolism is a prerequisite for bioprosthetic calcification. Systemic efforts to manipulate this variable have demonstrably reduced bioprosthetic calcification in animal models but have potentially serious ramifications through deleterious effects on bone metabolism [25]. Strategies for controlled release of antimineralization compounds in the vicinity of the valve might serve to reduce the systemic toxicity of this approach [26]. Certainly factors related to the bioprosthesis are involved in the initiation of calcification. A main focus for mitiga-

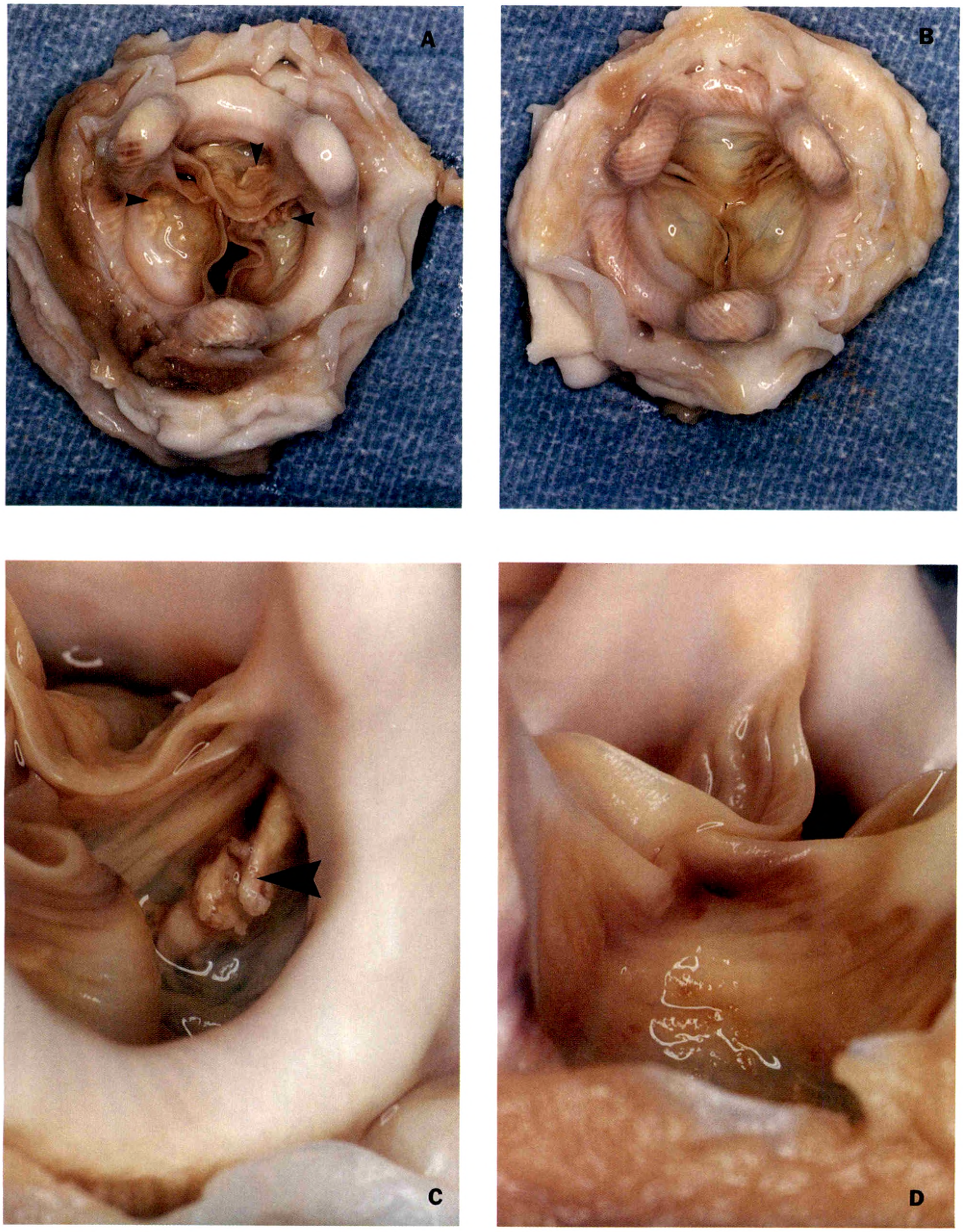

Fig 3. (A) Gross photograph of an explanted control valve demonstrating heavy calcification (arrows) *of all leaflets. (B) An 2-aminooleic acid–treated valve that is well endothelialized and free of any mineralization. (C) Closer view of a control valve leaflet with a large cuspal calcium deposit* (arrow). *(D) Close-up of pliable, deposit-free, 2-aminooleic acid–treated leaflet.*

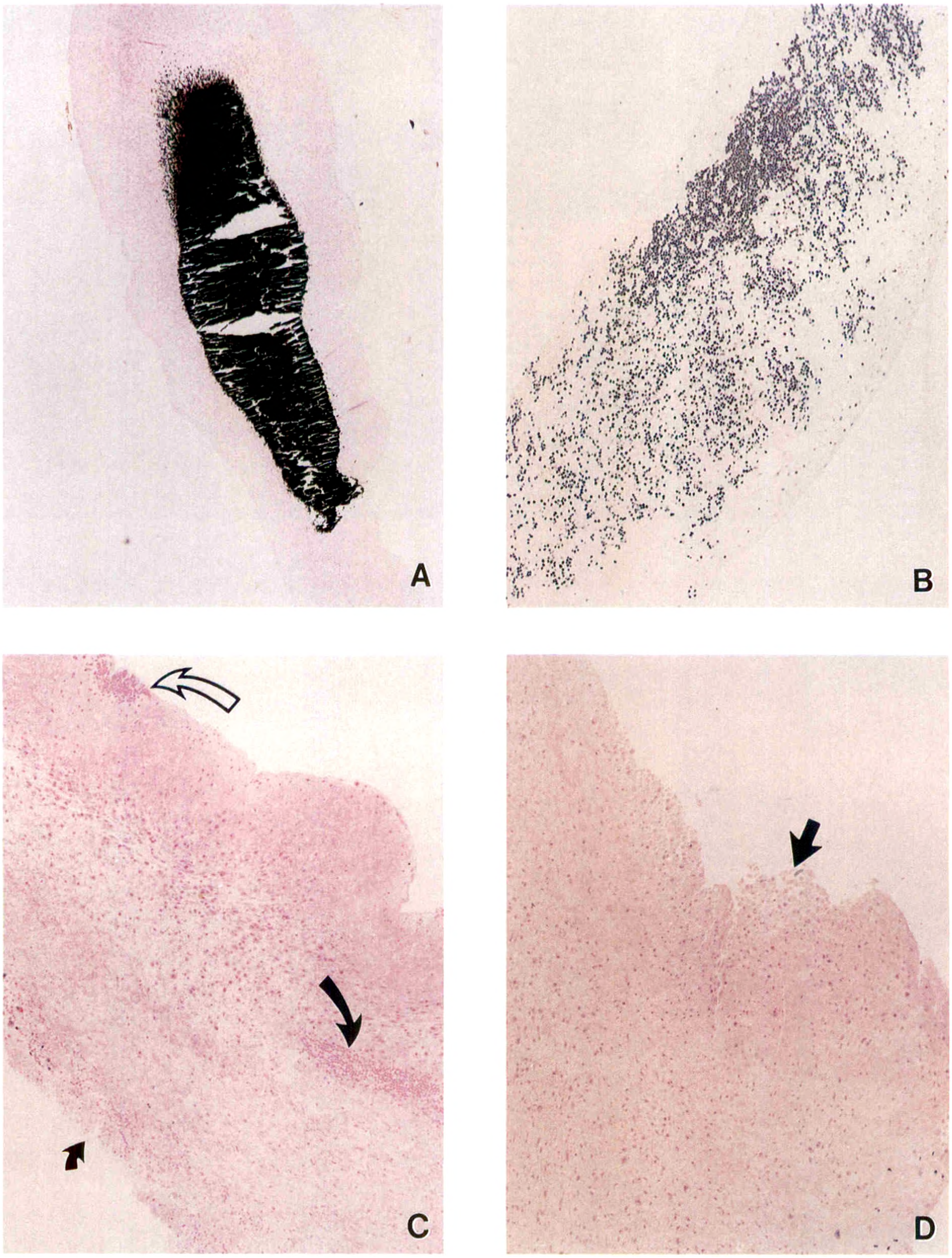

Fig 4. Light microscopic findings: (A) Control valve mineralization with large intrinsic calcific deposit. (Von Kossa stain [calcium phosphates black], ×50.) (B,C,D) Features of 2-aminooleic acid–treated valves: (B) Cuspal hematoma. (Movat stain, ×50.) (C) Generalized structural loosening, with superficial (open arrow) *and deep* (large filled arrow) *hematomas, and loss of surface integrity* (small filled arrow). *(Hematoxylin and eosin, ×50.) (D) Surface roughening and disruption* (arrow). *(Hematoxylin and eosin, ×100.)*

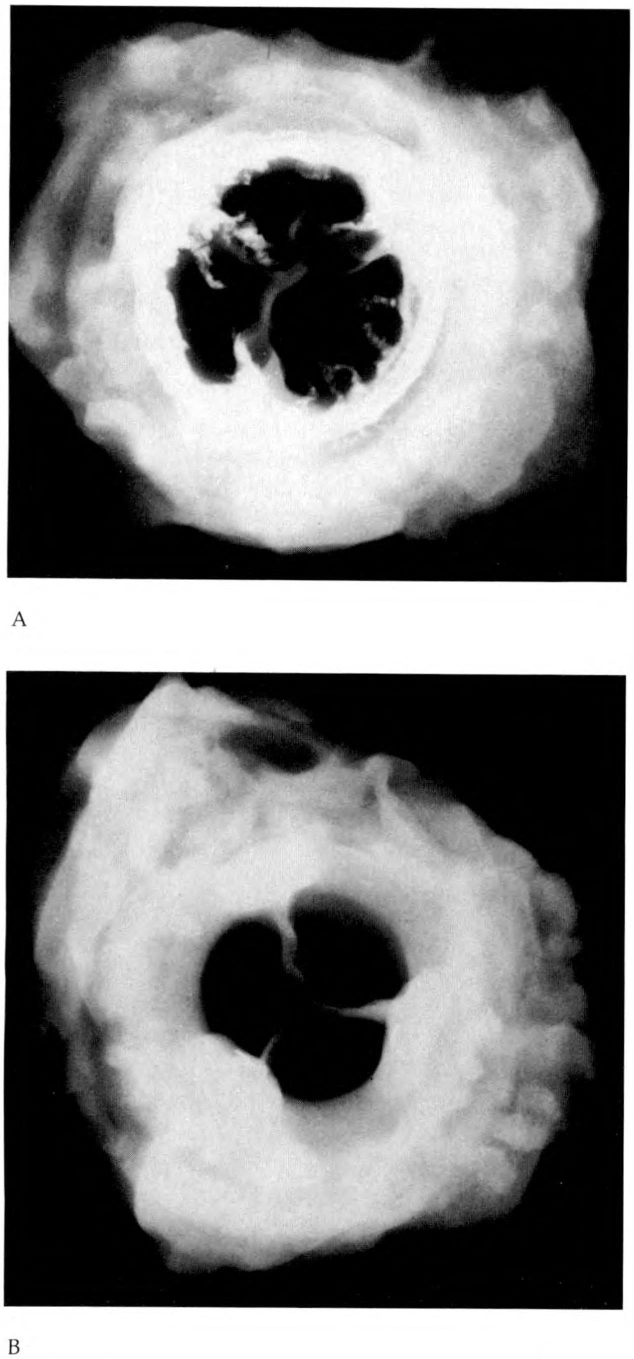

Fig 5. (A) Mammographic exposure of a control valve showing extensive areas of leaflet opacification corresponding to calcium deposition. (B) 2-Aminooleic acid–treated valve mammograph which is radiolucent, indicating freedom from calcification.

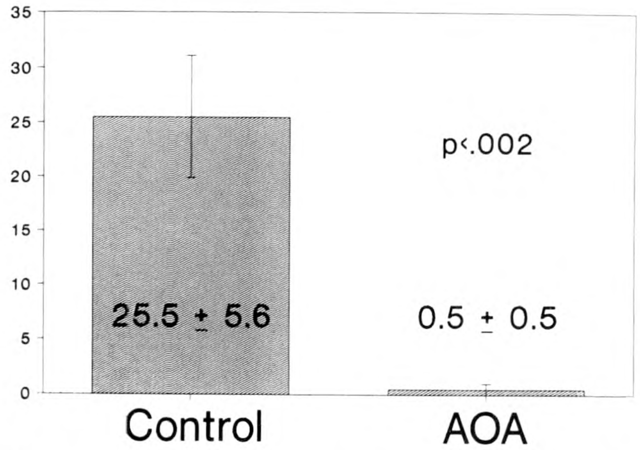

Fig 6. The mean radiographic scores for the two groups exhibiting the highly significant difference in calcium deposition (mean ± standard error). (AOA = *2-aminooleic acid.)*

tion of mineralization has been an attempt to modify chemically the preserved biological material in a preimplantation process. A broad range of compounds and treatment processes have demonstrated antimineralization efficacy in protecting implanted porcine aortic valves or bovine pericardial tissue. Various surfactants (sodium dodecyl sulfate [ie, T6], polysorbate-80, Triton X-100, *N*-lauryl sarcosine) [22], dyes (toluidine blue), impregnation techniques (polyacrylamide) [22], calcium binding or apatitic inhibitors (diphosphonates) [27], ionic antagonists (aluminum) [28], and other treatments have exhibited reduction of calcification in various animal models [22, 29, 30]. Thus, many different approaches to anticalcification by modification of the biological material have been devised and have yielded variable reduction of mineral deposition. Unfortunately, no anticalcification technique has yet been demonstrated to deter mineralization in the clinical setting [31].

As research efforts have focused on the problem of bioprosthetic calcification it has become apparent that the glutaraldehyde preservation process is a two-edged sword. Glutaraldehyde is used for tanning all currently available clinical bioprostheses. Carpentier and associates [32] demonstrated that glutaraldehyde pretreatment in the manufacturing process established a tissue valve sufficiently durable for clinical use. Glutaraldehyde was

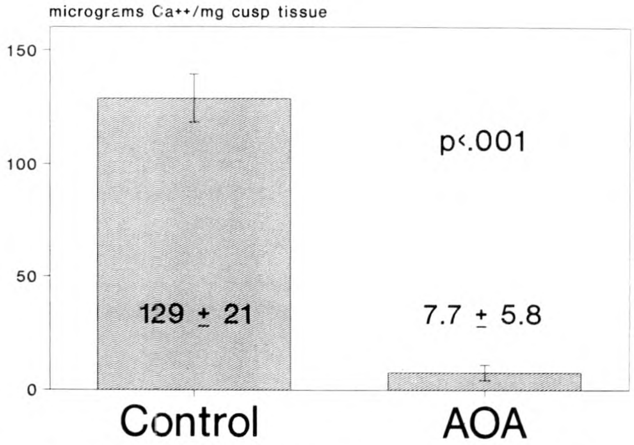

Fig 7. The mean quantitative leaflet calcium content of control and 2-aminooleic acid–treated (AOA) *valve groups is very significantly different (mean ± standard error).*

superior in this regard to formaldehyde. The glutaraldehyde-generated covalent cross-links between the bioprosthetic tissue collagen molecules explain the tensile advantage. Unfortunately, this same glutaraldehyde preservation method is a significant promoter of the bioprosthetic calcification process [23].

A new technique for bioprosthetic antimineralization was devised that takes advantage of the universal glutaraldehyde preservation technique for these devices. Using the free aldehyde groups associated with glutaraldehyde preservation, 2-aminooleic acid was covalently bound to porcine aortic leaflets and tested in the rat subcutaneous implant model [3]. These trials demonstrated essentially complete protection from calcification of the leaflets. The subsequent step in assessing anticalcification efficacy and possible clinical relevance and utility was large mammal testing of intact, treated valves. This anticalcification agent, 2-aminooleic acid, was applied in a proprietary process [3] after the manufacture of standard clinical quality and otherwise unmodified porcine bioprostheses. These valves were then tested in the mitral position in juvenile sheep.

Jones and associates [4–6] standardized and have extensive experience with a juvenile sheep model for chronic bioprosthetic valve implantation studies. The important feature of the model is the rapid calcification of standard porcine bioprostheses over weeks or months in a way that mimics the process that might take years in mature animals or humans. This allows timely acquisition of data on anticalcification treatments in clinically useful valve sizes and designs in an orthotopic position exposed to typical cyclical loading conditions and flows. Furthermore, Jones and colleagues [33] have demonstrated in these comparative studies that antimineralization efficacy in the small mammal subcutaneous implant model does not always correlate with efficacy in the chronic sheep intracardiac implants, thus emphasizing the need for this advanced screening methodology.

There was absolute concordance in all tests designed to measure the valvular calcification in this juvenile sheep study. There was a clear reduction and near elimination of mineralization documented for the treated valves by every test employed. The hemodynamic studies demonstrated the functional correlation of the degree of calcification with stenosis in the control valves and lower gradients and larger areas with the AOA valves. The simple examination and palpation of the explanted valves was sufficiently convincing regarding the anticalcification effect, but this was clearly nonquantitative.

To quantitate the difference in calcification between the two valve groups, two independent methods of determination were used. The x-ray examination of the valves was quantifiable and confirmed the success of AOA in preventing bioprosthetic mineralization. Previously described radiographic scoring techniques for assessment of bioprosthetic valve calcification were reviewed [33, 34]. A simple method was used that measured the size and number of calcium deposits without particular emphasis on topographical distribution, as in the detailed scoring system of Gallo and associates [34]. For this screening study the complexity of scoring systems directed partly toward determining patterns and possible etiology of calcification was unnecessary. These mammographic examinations confirmed the protection from calcification by AOA.

In addition to the x-ray score, a quantitative biochemical determination of leaflet calcium was made. This was the most rigorous and objective of the measures of success used in this study and was uniformly indicative of AOA protection compared with control valve calcium levels.

Although no gross valve failures were noted in the AOA valves, subtle signs of structural deterioration were apparent. These features appear to be related to the technical aspects of AOA treatment, as modification of AOA valve processing methodology has eliminated the valve surface roughening while preserving the anticalcification properties of AOA in the rat subcutaneous model [35]. The potential for toxicologic problems with AOA appears to be remote from the biocompatibility study data (on file, Biomedical Design, Inc). Furthermore, the compound is chemically similar to oleic acid, a normal component of human lipid metabolism. Although not yet tested in large mammal circulatory studies, this anticalcification process appears to hold promise for similar efficacy in pericardial bioprostheses [3].

Aminooleic acid treatment of porcine bioprostheses has demonstrated exceptional reduction of valvular tissue mineralization in a widely accepted animal model of accelerated bioprosthetic calcification. This process opens a novel avenue of study in the search for improved clinical bioprosthetic antimineralization.

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Biomedical Design, Incorporated, is the assignee of the patent for this antimineralization process. Dr Girardot is the co-owner of Biomedical Design, Inc. No other author has any financial interest in this method.

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Appendix 1. Table used for determining radiographic calcification scores

Calcium deposit size	>0–1mm	>1–2mm	>2–3mm	>3–4mm
Weighted score for each deposit by size	1	2	3	4
Leaflet				
1	x,x	. . .	x	. . .
2	x,x,x	x,x	. . .	x
3	x,x	x,x	. . .	. . .
Subtotals	7	8	3	4
Sum of all leaflet scores equals valve radiographic score				22

x = one calcium deposit corresponding to size range of column heading.

DISCUSSION

DR RICHARD E. CLARK (Pittsburgh, PA): Dr Michael Jones at the National Heart, Lung, and Blood Institute is the person who developed the juvenile sheep model for testing various valves, particularly those that use biologic tissues. Over the past 11 years he has implanted more than 1,500 heart valves in sheep. He was unable to be here and kindly consented to my request to show some of his data.

Data from more than 240 animals demonstrated the effects of various antimineralization treatments for porcine aortic valves and the lack of any salutory effects for bovine pericardial valves. Calcium content was determined by atomic spectroscopy, and was measured in milligrams per gram. There were a few treatments with very low calcium content after 20 weeks of implantation. Polysorbate-treated porcine valves had 7.6 mg of calcium per gram of tissue, which was the lowest value found. Dr Gott's findings when compared with the data of Dr Jones show that this new process results in calcium content as low as Dr Jones has been able to find in 10 years with a host of other treatments.

I would like to make a second comment on Dr Gott's paper and ask him a couple of questions. In data from a large series comprising 18 standard porcine valves and 15 treated by the PV2 process implanted into the mitral position in juvenile sheep for 20 weeks, there was a very wide distribution of calcium content for each valve treatment as a function of individual animals. Dr Gott showed similar data. This emphasizes the point that one needs a large number of complete experiments to determine if there is a high degree of efficacy. Dr Gott had only eight treated valves. If one takes the eight lowest values for standard valves from Dr Jones's experience, one might have made a different interpretation of the degree of efficacy of Dr Girardot's process.

The first question is, are you going to increase the number of animals in the study to determine the distribution of calcium content? The second question is, did the treatment alter the ultrastructure of collagen? Dr Victor Ferrans in the Pathology Branch at the National Heart, Lung, and Blood Institute and Dr Jones have been able to find that some anticalcification treatments affect the major collagen bundles, suggesting a destructive effect that may become manifest as decreased fatigue resistance to flexion. Have your explanted valves had ultrastructural analyses, and have nonimplanted valves been tested in a durability tester?

DR GOTT: In answer to your first question, indeed, we are excited enough in Dr Guyton's laboratory with this compound and this technique to pursue this further. We do plan another series of experiments to increase the number of animals with the treated valve that have been studied with the new modification of the technique. This modification appears to eliminate these structural problems.

With regard to the second question, no, these valves have not been studied at the ultrastructural level. However, they have been studied extensively at the light microscopic level. This was the only source of concern in the whole study, that is, the structural loosening and surface roughening that I mentioned in the treated valves. Again, this appears to have been remedied by a change in the technique for application of the AOA to the valve itself.

With regard to collagen chemistry or deformation or degradation or change related to the AOA treatment, I cannot comment specifically on that.

DR JACK W. LOVE (Santa Barbara, CA): Dr Gott and his colleagues have presented really impressive results with Dr Girardot's anticalcification treatment of porcine valves in the juvenile sheep model. This represents one more approach at attempting to retard calcification and improve durability of the xenograft valve. The issue of antigenicity of xenograft tissue as a determinant of calcification and durability has not been settled. Xenograft tissue after glutaraldehyde tanning retains some antigenicity. This was clearly shown by Carpentier and subsequent investigators. We have continued to pursue the concept of a nonantigenic, noncalcifying, more durable bioprosthesis made of autogenous tissue in the operating room at the time of operation for valve replacement.

Our valves are made in the operating room from a rectangle of pericardium treated with a 5-min immersion in 0.6% glutaraldehyde. The valve can be fabricated in about 5 minutes. We have implanted these valves in the juvenile sheep model for 5 months, 20 weeks, with no other treatment of the tissue. These valves are competent by ventricular injection at cardiac catheterization, the hemodynamics are normal, the tissue is soft and pliable, and the valves are not calcified.

Dr Gott, have you looked at the antigenicity of your treated and your untreated valves?

DR ROBERT W. M. FRATER (Bronx, NY): I do not think you answered Dr Clark's question, which is, have you tested these devices in the wear tester after treating them with the AOA, and do you have a notion of what is happening to the valve and to the glutaraldehyde portion of it when you treat it with AOA?

FROM THE AUDIENCE: Is the AOA chemically bound, or could it be that the 20-week test, accelerated test of calcification, is also an accelerated test of washout? It may be in the clinical situation the AOA will not be there in 2 years when we really need it.

DR GOTT: I apologize for not answering Dr Clark's question about the mechanical wear testing as Dr Frater pointed out. The new treatment, the modification of the AOA treatment, has been tested in a mechanical cycle device in more than 50 million cycles, which corresponds to years of human cardiac cycling, and it does appear that there is no mechanical problem with the valve.

With regard to the antigenicity question, in the literature there appears to be some ambiguity about whether the T or B cell function plays a role in the calcification of these valves. The answer is not quite clear. That is a fascinating valve that you made there in the operating room. In answer to the specific question, no, we did not look for any elements of antigenicity in our model. The only thought we had about antigenicity was that we used bovine source heparin rather than porcine heparin when we placed the valves.

With regard to the chemical properties of AOA and the interaction with the valve, again, this is speculation, but the compound is designed to have a covalent link with the valve, and it appears in rat subcutaneous washout studies that the compound does remain bound significantly to the valve tissue over weeks and months.

Granulocyte Sequestration and Early Failure in the Autoperfused Heart-Lung Preparation

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We investigated the role of pulmonary granulocyte sequestration in the development of early failure of the autoperfused working heart-lung preparation. A significant decline in the total circulating leukocyte count in 21 preparations at 60 minutes of perfusion (5.0 to 1.4 × $10^3/\mu L$; 28% of baseline; $p < 0.001$) was observed. Differential cell counts in 14 of these preparations revealed a predominant decrease in granulocyte count (8.7% of baseline) and a moderate decline in lymphocyte count (46% of baseline). In study I, indium 111–labeled autologous granulocytes were injected intravenously into 10 adult New Zealand White rabbits. In group I ($n = 5$), an autoperfused working heart-lung preparation was harvested and perfused for 60 minutes. In group II (controls, $n = 5$), the heart-lung block was harvested following 60 minutes of in situ perfusion. Organ blocks were imaged before and after saline flush. There was a significant decline in granulocyte counts at 60 minutes of perfusion in group I versus no change in group II (I, 2.3 ± 0.4 to 0.3 ± 0.1; $p < 0.01$; II, 1.7 ± 0.2 to 2.3 ± 0.5; not significant; $\times 10^3/\mu L$ ± standard error of the mean). Postflush lung activity was significantly increased in group I versus group II (I, 3,751 ± 566; II, 1,867 ± 532; $p < 0.05$; counts ± standard error of the mean). In study II, 15 autoperfused preparations were divided into two groups. Group I ($n = 10$) preparations were controls. Group II ($n = 5$) animals were depleted of leukocytes by pretreating with nitrogen mustard. Group I (controls) produced a bimodal survival distribution (Ia, 8.2 ± 1.0; Ib, 26.4 ± 2.0; hours ± standard error of the mean). Group II survival was significantly longer than that of group Ia and similar to that of group Ib (II, 25.3 ± 2.2; $p < 0.01$ versus group Ia, not significant versus group Ib; hours ± standard error of the mean). Hemodynamic profiles for group II closely paralleled those of group Ib. In conclusion, pulmonary sequestration of granulocytes occurs early in the autoperfused working heart-lung preparation (within 60 minutes of autoperfusion), and preoperative leukocyte depletion prolongs survival of the autoperfused working heart-lung preparation by eliminating the subset group Ia (short survivors) seen in untreated preparations.

(Ann Thorac Surg 1992;53:217–26)

Clinical application of organ transplantation has increased interest in the development of effective means of organ preservation [1–3]. Methods of preservation of the heart and lungs for transplantation have developed along two distinct lines: hypothermic suppression of organ metabolism and autoperfusion. Because complete metabolic suppression is impossible at this time, current methods merely minimize the inevitable ischemic cellular damage. The autoperfused working heart-lung preparation has the theoretical advantage of eliminating ischemia and prolonged preservation.

The concept of the autoperfused preparation was first described by Martin in 1883 [4]. It was first used as an experimental model by Starling in 1918 [5]. In 1948, the Russian surgeon Demikhov [6] used the "live" preparations to preserve heart grafts for transplantation. This model has been refined further by Robicsek and associates [3], whose work established the autoperfused heart-lung preparation as a reliable method for ex vivo preservation of the heart and lungs for 20 hours. Hardesty and Griffith [7] have successfully used this method clinically.

A true understanding of the autoperfused preparation has been unfolding slowly. Work by Kontos and coworkers [8] and Robicsek and colleagues [9] has clearly demonstrated the need for substrate enhancement to extend organ survival. The eventual failure of the preparation is a complex problem. Multiple factors, including cellular elements, lipid mediators, peptides, and denervation, have been implicated [10–12]. Studies have shown that cardiac function is preserved satisfactorily in the autoperfused preparation [8, 9, 12]. Pulmonary function appears to deteriorate more rapidly than cardiac function. Manifestations of pulmonary edema or pulmonary hypertension are often seen as the terminal event [10–13]. Attempts at prolonging survival of the autoperfused preparation and therefore enhancing its clinical usefulness have led to a variety of approaches including pretreatment with lipid mediator blockers, complement activation inhibitors, and steroids [11, 12, 14]. Attempts have also been made to alter the perfusate [12].

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The early events surrounding the initiation of the autoperfused, working heart-lung preparation may set the stage for its ultimate failure. Studies in our laboratory have documented a dramatic early decrease in circulating leukocytes, predominantly granulocytes. To further investigate the role of granulocyte sequestration in the early stages of the autoperfused preparation, we conducted two studies. In study I, granulocytes were labeled with indium 111 and the autoperfused preparations were established. In study II, animals were depleted of leukocytes preoperatively to determine if survival could be prolonged.

Material and Methods

Study I

Ten New Zealand white rabbits weighing 3.4 ± 0.2 kg were premedicated with xylazine (10 mg/kg) and anesthetized with acepromazine (0.25 mg/kg) and ketamine (25 mg/kg). Additional pentobarbital in increments of 1 mg/kg was administered as needed. A tracheostomy was performed and mechanical ventilation was begun with a rodent ventilator (Harvard model 680, with room air; tidal volume of 5 to 6 mL/kg; respiratory rate of 30 breaths per minute). The right internal jugular vein was cannulated with a 16-gauge angiocatheter (Deseret Medical) and blood was collected for granulocyte labeling. Limb leads were used to monitor the electrocardiogram.

Autologous granulocytes were labeled with indium 111 and reinjected intravenously into the intact animal. In all animals, the labeled granulocytes circulated for 30 minutes, and then the animals were heparinized (100 units/kg) and divided into two groups. In group I (n = 5), an autoperfused, working heart-lung preparation was established. A median sternotomy was performed and the aortic arch vessels as well as the superior and inferior venae cavae were isolated. The venous inflow line was established by placing intravenous tubing through the right superior vena cava into the right atrium. The arterial outflow line was established by ligating the aortic arch vessels and cannulating the brachiocephalic artery with intravenous tubing. Inflow and outflow lines were attached to the reservoir (300 mL Transfer pack container, Fenwal, Deerfield, IL), which was primed with 50 mL of normal saline solution (Fig 1). Total perfusion through the circuit was instituted by filling the reservoir under arterial pressure while ligating the distal aorta, superior vena cava, and the inferior vena cava. Approximately 100 mL of autologous blood was collected in the process of instituting the circuit. Once the autoperfused, working heart-lung preparation was established, the ventilatory rate was decreased to 5 breaths per minute. The autoperfused preparation was then extracted and allowed to function for 60 minutes. Total time of circulation of the labeled granulocytes was 90 minutes.

Group II (n = 5) animals were cannulated in a similar manner to group I; however, the heart and lungs remained in situ. Labeled granulocytes were again allowed to circulate for a total of 90 minutes before sacrifice of these animals.

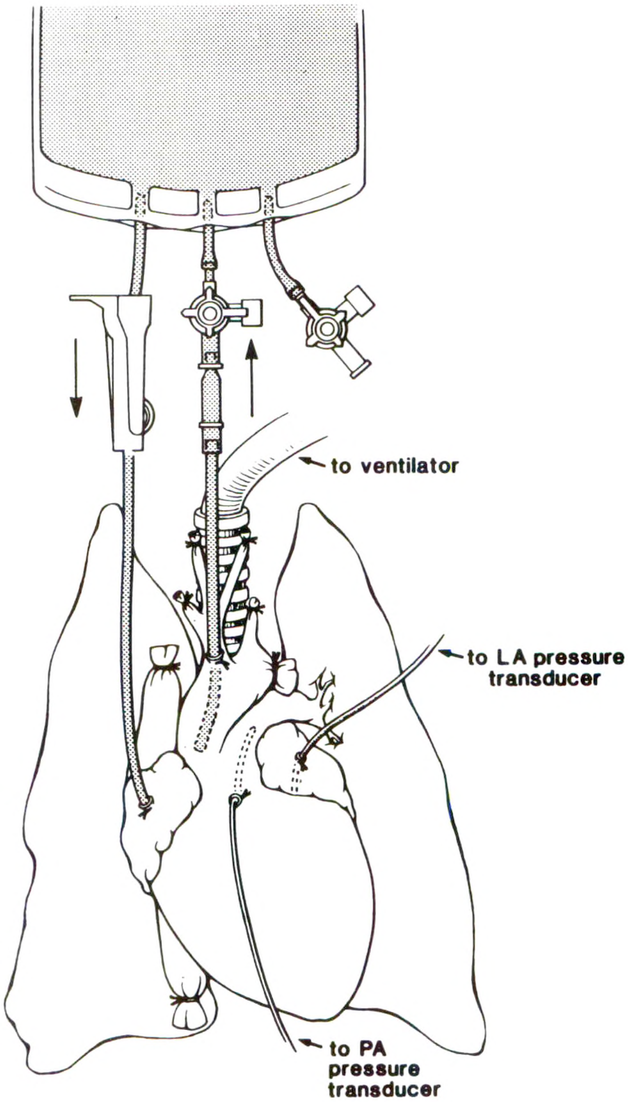

Fig 1. The autoperfused, working heart-lung preparation. (LA = *left atrial;* PA = *pulmonary artery.)*

INDIUM 111 GRANULOCYTE LABELING. Autologous rabbit venous blood (8.4 mL) was drawn from the rabbits, anticoagulated with acid citrate dextrose (1.6 mL), and sedimented with 10 mL of Hespan (DuPont, Wilmington, DE). The supernatant was withdrawn and centrifuged at 250 *g* for 5 minutes to yield a white cell button, which was resuspended in 2 mL of normal saline solution and 2 mL of plasma. This suspension was layered onto 3 mL of Lymphoprep (NYCOMED AS, Oslo, Norway) and centrifuged at 800 *g* for 15 minutes. This resulted in a pellet of approximately 50% granulocytes and 50% red cells, which was resuspended in 1 mL of normal saline solution. Because red cells label with much less affinity than granulocytes, this contamination was not considered to be significant [15]. Platelet contamination was minimal.

This cell suspension was labeled with 200 to 400 μCi of indium oxine ^{111}In complex and allowed to incubate for 20 minutes. The suspension was then centrifuged at 250 *g* for 5 minutes. The supernatant was removed and the labeled granulocytes were resuspended in 3 mL of autologous plasma. The labeled granulocytes (140 to 300 μCi) were then reinjected into the venous circulation of the rabbits at time = −30 minutes.

SCINTIGRAPHY. Imaging was performed using a standard field of view gamma camera (Technicare 400) with a medium energy collimator and 20% windows centered on the 171 and 247 keV photopeaks. Anterior whole-organ block images were acquired in a 64 × 64 computer matrix. Initial static scans of the organ blocks were performed in a blood-inclusive manner (4-minute scan). The organ blocks were then flushed with normal saline solution and reimaged. Regions of interest were drawn around the heart and the lungs. Total counts for each region were established.

EXPERIMENTAL DESIGN. Group I preparations were allowed to function for 60 minutes and were then terminated (time = 60 minutes) by injecting a lethal dose of pentobarbital (100 to 300 mg). Once the heart stopped beating, the inflow and outflow lines were closed, and the initial blood-inclusive scans were performed. The aortic outflow line was then opened, and the organ block was flushed via the inflow line. The flush consisted of normal saline solution at 100 mL/minute for 2 minutes. Once clear of blood, the organ blocks were reimaged. Group II animals were cannulated in a similar manner to group I and sacrificed 60 minutes after heparinization (time = 60 minutes) with pentobarbital (100 to 300 mg). The organ blocks were then extracted and, again, the initial blood-inclusive scans performed. The organ blocks were flushed in an identical manner to group 1 and reimaged.

Samples of venous blood for complete blood cell count with differential were collected from both groups 5 minutes before infusion of labeled granulocytes (time = −35 minutes), 5 minutes after infusion of labeled granulocytes (time = −25 minutes), before heparinization (time = −5 minutes), 5 minutes after heparinization (time = 0 minutes), and finally at sacrifice of group II animals or termination of group I autoperfused preparations (time = 60 minutes). In group I, blood was also collected at time = 5 minutes and time = 15 minutes, 5 and 15 minutes after establishing the autoperfused preparation, to show the dynamic nature of the changes in circulating granulocytes. Leukocyte counts were corrected for hemodilution according to the formula: corrected concentration = measured concentration × initial hemoglobin/hemoglobin during perfusion.

Study II

In the second study, 15 autoperfused working heart-lung preparations were established as previously described and divided into two groups. Group I (n = 10) were untreated autoperfused preparations. Group II (n = 5) were leukocyte depleted by pretreating the animals with 1.7 mg/kg mechlorethamine HCl 72 hours before establishing the autoperfused preparation. Group II animals were heparinized with 10 units/kg instead of 100 units/kg owing to excessive bleeding at 100 units/kg.

The autoperfused, working heart-lung preparation was then instrumented as follows: high-fidelity micromanometer catheters (MPC-500; Millar Instruments, Inc, Houston, TX) were placed into the pulmonary artery and left atrium. Also, fluid-filled catheters were attached to the inflow line, outflow line, and the tracheal cannula to monitor aortic, central venous, and intratracheal pressure, respectively. Output from the multichannel recorder (Hewlett Packard 4568c, Andover, MA) was digitized and acquired at a rate of 50 Hz onto a personal computer (Data 286; Dataworld Inc; Pico Rivera, CA) using Asystant+ software (Asystant Software Technologies, Rochester, NY). Once fully instrumented, the autoperfused preparation was then suspended from the tracheal cannula and placed into a humidified chamber maintained at 25°C. The reservoir height was adjusted to maintain an initial systolic blood pressure of 65 ± 5 mm Hg. The inflow was adjusted to establish an initial pulmonary artery pressure of 4.0 ± 0.5 mm Hg.

Data collected hourly for the first 12 hours included central venous, aortic, pulmonary artery, left atrial, and intratracheal pressure, as well as cardiac output. Cardiac output was determined by measuring aortic ejection volume for 30 seconds through a three-way stopcock positioned in the outflow line. After the initial 12 hours, hemodynamic data were collected continuously.

Blood was collected for complete blood counts with differential at time −1, 1, 3, 6, and 12 hours of perfusion. Leukocyte counts were corrected for hemodilution. Blood glucose level was monitored each hour for the first 12 hours, and the perfusate was supplemented if the glucose level fell to less than 5.5 mmol/L (100 mg/dL). Arterial blood gases were obtained at 1, 6, and 12 hours of perfusion.

EICOSANOID ANALYSIS. Blood samples for eicosanoid analysis were collected at −1, 1, 6, and 12 hours. Samples (1.5 mL) were placed into glass tubes containing potassium ethylenediaminetetraacetic acid (0.06 mL of 7.5% solution) and sodium indomethacin (24 μg/mL whole blood) and immediately placed in a 4°C ice bath. At the conclusion of the experiment samples were centrifuged at 1,900 *g* for 25 minutes at 4°C. Plasma was separated by bulb aspiration, placed into polypropylene tubes, and frozen at −80°C until radioimmunoassay was performed. Stable metabolites of thromboxane A_2 and prostacyclin were measured by standard double antibody radioimmunoassay [16]. Values are reported in picograms per milliliter.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

STATISTICAL ANALYSIS. Values are reported as mean ± standard error of the mean. Comparisons in study I were made using Student's *t* test with a *p* value less than 0.05 considered significant. In study II mean survival was analyzed by the Peto-Wilcoxon test. Comparisons between groups (pulmonary artery pressure, left atrial pressure, compliance, leukocyte counts, and platelet counts) were analyzed using repeated-measures analysis of variance. Comparisons within groups were analyzed using

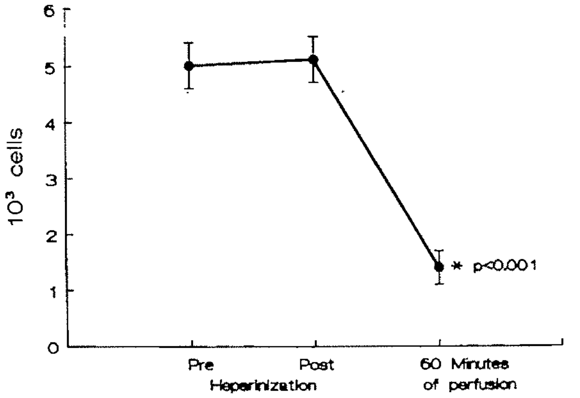

Fig 2. Leukocyte counts in autoperfused heart-lung preparation (n = 21). (p < 0.001, counts at 60 minutes of perfusion versus before or after heparinization of the intact animal.)*

two-way analysis of variance. Levels of 11-dehydothromboxane were analyzed using the Mann-Whitney test. In all cases differences were considered significant at p less than 0.05.

Results

Study I

LEUKOCYTE COUNT. A marked decrease in the leukocyte count was evident upon instituting the autoperfused, working heart-lung preparation. In our prior study of 21 rabbit autoperfused preparations, the leukocyte count was found to decrease from 5,000 ± 400/µL to 1,400 ± 300/µL at 60 minutes of autoperfusion ($p < 0.001$)(Fig 2). Differential counts were done using a hematology analyzer (NE 5000). In 14 of these preparations, differential leukocyte counts revealed a predominant granulocyte depletion (Fig 3). Lymphocyte total counts decreased as well, but their percentage of the total leukocyte count increased from 55% ± 2.3% to 83% ± 2.8% ($p < 0.001$).

In study 1, a similar pattern of leukosequestration was evident. Initial granulocyte counts in groups I and II were similar. Upon institution of the autoperfused preparation (group I), the granulocyte count significantly fell to 17% of baseline at 15 minutes of perfusion and further decreased to 13% ($p < 0.001$) of baseline at 60 minutes of perfusion. In marked contrast, group II animals showed no significant change in the granulocyte count at the termination of the experiment (group I, 2.3 ± 0.4 to 0.3 ± 0.1; $p < 0.001$; group II, 1.7 ± 0.2 to 2.3 ± 0.5; not significant [NS]; × 10^3/µL ± standard error of the mean; time = 60 minutes) (Fig 4). The differential leukocyte count revealed the typical pattern of increasing lymphocyte percentage in group I, whereas group II showed no change.

INDIUM 111 AUTOLOGOUS GRANULOCYTE SCANS. The total circulating time of the labeled granulocytes was 90 minutes in both groups. Total counts in the region of the lungs and heart of the intact organ blocks as well as the postflush count are shown in Table 1. The counts have been corrected to 100 µCi.

Initial counts in the region of the lungs were not significantly different between group I and group II (4,729 ± 630 versus 3,741 ± 485; NS). Postflush scans were quite different. Group I autoperfused preparations retained approximately 80% of their initial activity, whereas group II controls retained less than 50% (group I, 3,751 ± 566 versus group II, 1,867 ± 531; $p < 0.05$)(Fig 5). The activity in the region of the heart showed a different initial pattern. Group I, the autoperfused preparation, had decreased activity (group I, 1,035 ± 104 versus group II, 2,475 ± 330; $p < 0.01$)(Fig 6). This was believed to be due to early sequestration of labeled cells in the lungs of the autoperfused, working heart-lung preparation, and thus there was a decreased amount of activity in the circulating blood volume. Flushing cleared this blood volume, and the postflush heart activities were not significantly different (group I, 255 ± 46 versus group II, 370 ± 44; NS). Retention of activity in the lungs of group I as distinguished from group II is clearly seen in the scans (Figs 7, 8).

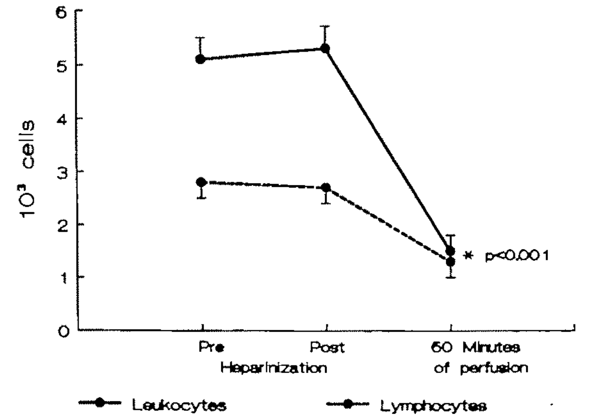

Fig 3. Differential counts in autoperfused heart-lung preparation (n = 14). (p < 0.001, lymphocyte and total leukocyte counts at 60 minutes of perfusion versus before or after heparinization of the intact animal.)*

Study II

SURVIVAL. Failure of the preparations was defined as the inability to maintain a systolic blood pressure of

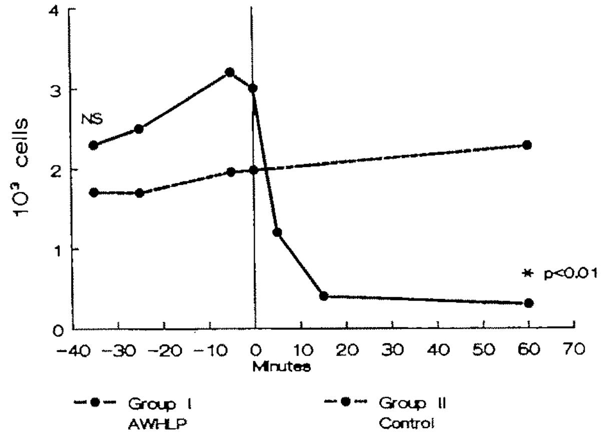

Fig 4. Granulocyte counts for study I (group I [AWHLP], autoperfused, working heart-lung preparation; group II, control). (p < 0.01, group I versus group II at 60 minutes of perfusion.)*

Table 1. Corrected Activity Counts in Study I

	Group I				Group II			
	Lung		Heart		Lung		Heart	
Preparation No.	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	4,323	3,274	700	174	3,877	735	1,778	322
2	4,635	3,378	905	208	4,494	2,898	1,954	541
3	2,778	2,311	1,148	178	3,494	2,126	3,146	324
4	5,267	4,075	1,283	413	2,033	518	3,391	295
5	6,641	5,718	1,140	301	4,804	3,059	2,106	369
Mean	4,729	3,751	1,035	255	3,741	1,867	2,475	370
SEM	630	566	104	46	485	531	330	44

Post = after flush; pre = before flush; SEM = standard error of the mean.

50 mm Hg with forward flow or depletion of the autologous blood reservoir. Group I controls produced a bimodal survival distribution (group Ia [n = 5], 8.2 ± 1.0; group Ib [n = 5], 26.4 ± 2.0; hours = standard error of the mean). Group II (leukocyte depleted) survival paralleled that of group Ib (25.3 ± 2.2; hours ± standard error of the mean; $p < 0.01$ versus group Ia, NS versus group Ib)(Fig 9).

HEMODYNAMIC. Autoperfusion was begun as described previously by adjusting the initial inflow to establish a pulmonary artery pressure of approximately 4 mm Hg. The reservoir height was adjusted to establish an initial systolic pressure of 65 ± 5 mm Hg. Hourly determination of pulmonary artery and left atrial pressure showed no significant differences between group Ia, group Ib, and group II.

PULMONARY ARTERY PRESSURE. The pulmonary artery pressure in all groups was initially set at 4.0 ± 0.5 mm Hg. In all groups, the pulmonary artery pressure rose over time, yet in group Ia it appeared to rise more rapidly than in group Ib and group II, although this was not significant.

LEFT ATRIAL PRESSURE. The initial left atrial pressure rose in all groups over time, although in group Ia again it appeared to rise more rapidly. In group II (leukocyte depleted), the left atrial pressure was unchanged for the first 12 hours and then rose over time.

CARDIAC OUTPUT. Cardiac output was determined by measuring the aortic ejection volume for 30 seconds with a three-way stopcock positioned in the outflow line. The initial cardiac output was variable among individual preparations with a range from 10 to 25 mL/min. Once established, the cardiac output was maintained essentially unchanged until failure of the preparation. The initial cardiac outputs were similar (group Ia, 18.7 ± 3.0; group Ib, 13.8 ± 1.5; and group II, 16.4 ± 1.6 mL/min; NS).

COMPLIANCE. Pulmonary compliance was calculated by the formula: tidal volume/change in intratracheal pressure. In all groups, compliance decreased over time. In group Ia, the initial compliance was 22.6 ± 3.8 mL/cm H_2O and decreased to 13.9 ± 3.8 mL/cm H_2O at 6 hours. In group Ib (long survivors), the initial compliance was 11.0 ± 2.3 mL/cm H_2O and decreased to 8.6 ±1.2 mL/cm

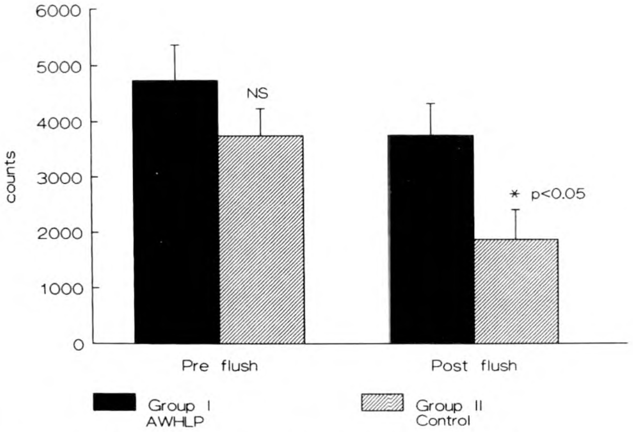

Fig 5. Lung activity counts, corrected to 100 μCi (group I [AWHLP], autoperfused, working heart-lung preparation; group II, control). (Preflush activity, group I versus group II, not significant [NS]; postflush activity, group I versus group II, $p < 0.05$.*)*

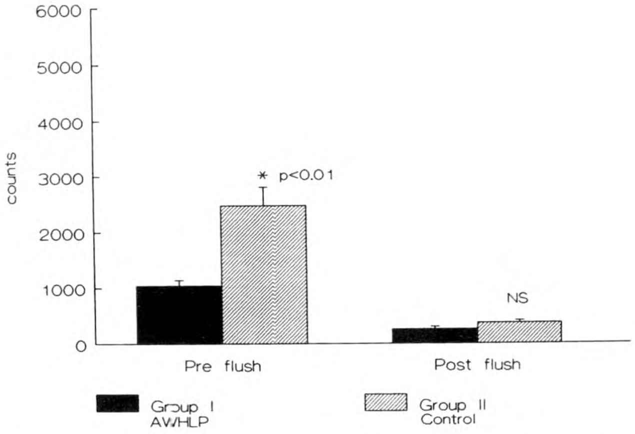

Fig 6. Heart activity counts, corrected to 100 μCi (group I [AWHLP], autoperfused, working heart-lung preparation; group II, control). (Preflush activity, group I versus group II, $p < 0.01$*; postflush activity, group I versus group II, not significant [NS].)*

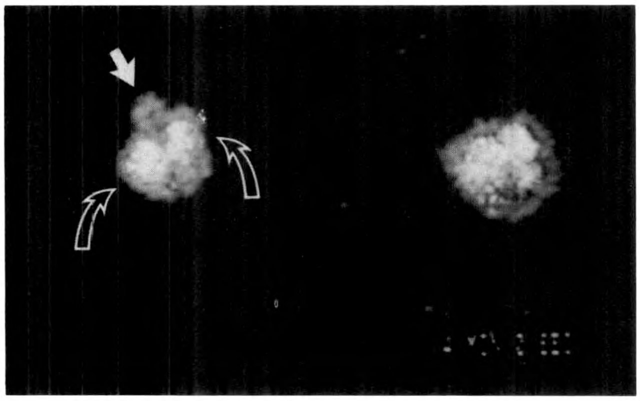

Fig 7. Indium-labeled granulocyte scan of group I autoperfused, working heart-lung preparation. Left scan is preflush scan of heart-lung block. Solid arrow *designates the region of the heart.* Hollow arrows *designate the region of the lungs. Right scan is the postflush scan. The preflush scan demonstrates greatest activity in the region of the heart, the blood volume.*

H_2O at 6 hours, 9.0 ± 1.8 mL/cm H_2O at 12 hours, and 6.8 ± 1.3 mL/cm H_2O at 20 hours. Pulmonary compliance in group II was initially 15.3 ± 2.0 mL/cm H_2O and decreased to 7.7 ± 1.4 mL/cm H_2O at 6 hours, 7.6 ± 1.6 mL/cm H_2O at 12 hours, and 4.8 ± 1.0 mL/cm H_2O at 20 hours.

ARTERIAL OXYGEN. Arterial blood gases were obtained at 1, 6, and 12 hours of perfusion. All groups were able to adequately oxygenate throughout the course of the preparation when ventilated with room air. In group Ia, the measured arterial oxygen tension was 142 ± 6 mm Hg at 1 hour and 127 ± 11 mm Hg at 6 hours. In group Ib, the measured arterial oxygen tension was 130 ± 12 mm Hg at 1 hour, 130 ± 11 mm Hg at 6 hours, and 127 ± 13 mm Hg at 12 hours. In group II, the measured arterial oxygen tension was 156 ± 3 mm Hg at 1 hour, 150 ± 4 mm Hg at 6 hours, and 145 ± 8 mm Hg at 12 hours.

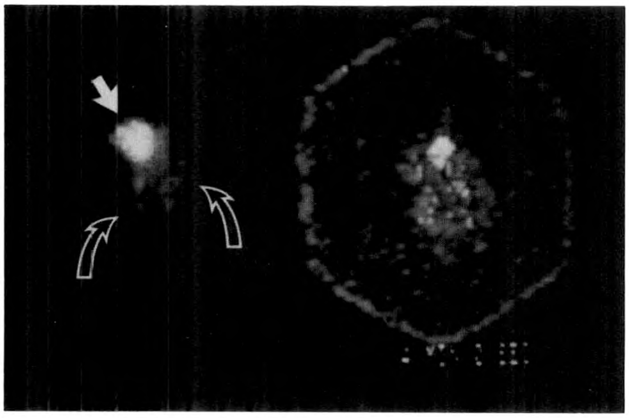

Fig 8. Indium-labeled granulocyte scan of group II (controls). Left scan is preflush scan of heart-lung block. Solid arrow *designates the region of the heart.* Hollow arrows *designate the region of the lungs. Right scan is the postflush scan. The preflush scan demonstrates greatest activity in the region of the lungs with retention of this activity after the flush.*

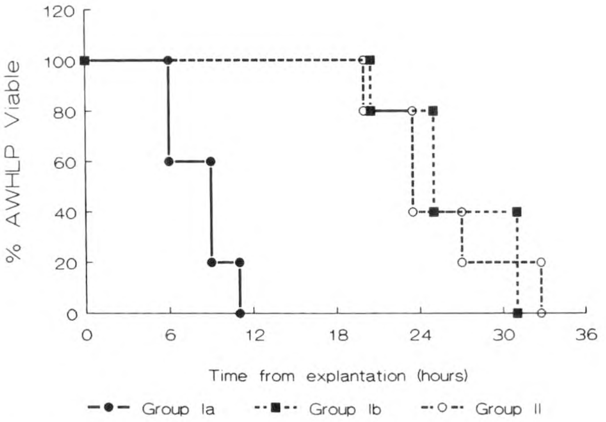

Fig 9. Survival curves for study II (group Ia, untreated short survivors; group Ib, untreated long survivors; group II leukocyte depleted). (AWHLP= autoperfused working heart-lung preparation.) ($p <$ *0.01, group II versus group Ia.)*

LEUKOCYTES. The initial leukocyte counts of group Ia, short survivors, and group Ib, long survivors, were similar (3.7 ± 0.7 versus 5.3 ± 0.8 × $10^3/\mu L$; NS) and different from group II leukocyte-depleted preparations (0.8 ± 0.1 × $10^3/\mu L$; $p < 0.01$ versus group Ia and Ib). In all groups, there was a significant decline in the leukocyte count upon establishment of the autoperfused working heart-lung preparation. In group Ia, the count decreased to 0.7 ± 0.2 × $10^3/\mu L$ at 1 hour of perfusion and increased slightly at 6 hours of perfusion to 1.3 ± 0.4 × $10^3/\mu L$. In group Ib, the count decreased to 2.5 ± 0.4 × $10^3/\mu L$ at 1 hour of perfusion and remained steady at 6 hours of perfusion at 2.5 ± 0.9 × $10^3/\mu L$. In group II, the count decreased to 0.2 ± 0.05 × $10^3/\mu L$ at 1 hour of perfusion and returned to baseline at 6 hours of perfusion 0.6 ± 0.05 × $10^3/\mu L$ (Fig 10). In all groups, the leukocyte counts dropped significantly upon institution of the autoperfused preparation. The leukocyte counts stabilized after the initial decline and were unchanged for the remainder of perfusion.

PLATELETS. The initial platelet counts in group Ia and group Ib were similar (240 ± 22 versus 340 ± 46 × $10^3/\mu L$; NS). Platelet counts in group II were similar to group Ia, yet different from group Ib (171 ± 33 × $10^3/\mu L$; $p < 0.05$ versus group Ib and NS versus group Ia). The lower platelet count in group II, the nitrogen mustard–treated animals, was most likely due to bone marrow suppression. In all three groups, there was a significant decrease in the platelet counts after heparinization. Marked thrombocytopenia was seen in one or two preparations in each group, thus accounting for this observation. After the initial decrease, the preparations show no further change in platelet counts over time (Fig 11).

EICOSANOID SYNTHESIS. The stable metabolite of thromboxane A_2, 11-dehydrothromboxane B_2, was measured preoperatively, as well as at 1, 6, and 12 hours of perfusion. Preoperative values in all three groups were similar. Group Ia (short survivors) demonstrated a dramatic rise at

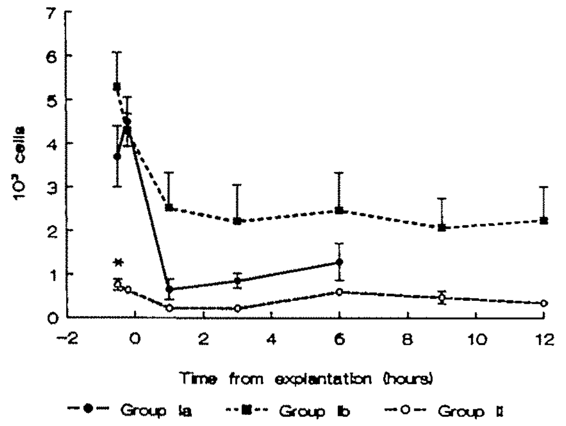

Fig 10. Leukocyte counts in study II autoperfused, working heart-lung preparations (group Ia, untreated short survivors; group Ib, untreated long survivors; group II, leukocyte depleted). (Initial leukocyte count, p < 0.01 for group II versus group Ia and group Ib.)

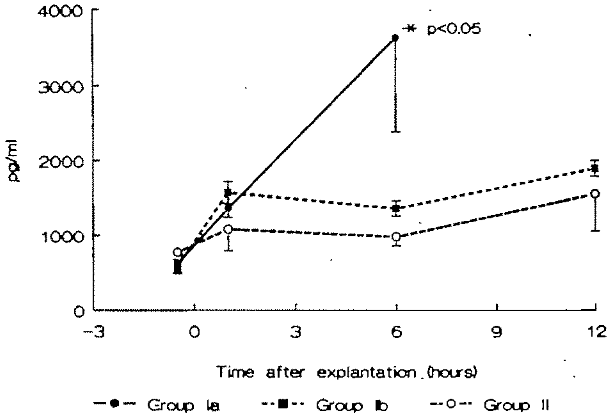

Fig 12. 11-Dehydrothromboxane B_2 in study II autoperfused, working heart-lung preparations (group Ia, untreated short survivors; group Ib, untreated long survivors; group II, leukocyte depleted). (p < 0.05 group Ia versus group II and for group Ia versus group Ib.)*

6 hours of perfusion (3,633 ± 1,248 pg/mL; $p < 0.05$ versus group II and $p = 0.05$ versus group Ib). Values in group Ib and group II gradually increased over time and ran a similar course (Fig 12).

Comment

Autoperfusion has been used for preparation of the heart and lungs for transplantation. This technique has since been abandoned clinically, in part because of inconsistent survival of the autoperfused organ blocks. Failure of this preservation method is often heralded by pulmonary hypertension with or without pulmonary edema [10–13]. The transition period from the intact animal to the ex vivo autoperfused, working heart-lung preparation is a critical time. Our work and that of others has shown a significant decline in leukocyte count upon institution of the autoperfused preparation [10, 14, 17]. These present studies focused on this phenomenon of leukosequestration and its potential role in the early failure of the autoperfused working heart-lung preparation.

In study I, indium 111-labeled granulocytes were used to document pulmonary leukosequestration. Indium 111 is a preferable labeling technique because of the stability of the label once it is attached to the leukocyte [18]. Leukocytes labeled with indium 111 have also been shown to retain their viability [19]. We chose to label granulocytes because of documented preferential depletion of granulocytes from the circulating blood volume of the autoperfused working heart-lung preparation [17]. In both groups, we allowed the labeled granulocytes to circulate for 30 minutes to equilibrate. In group I autoperfused preparations the typical decline in the granulocyte counts was evident upon the establishment of autoperfusion. Counts decreased by 83% within the first 15 minutes of perfusion. In group II controls, no such decline in granulocyte counts was demonstrated.

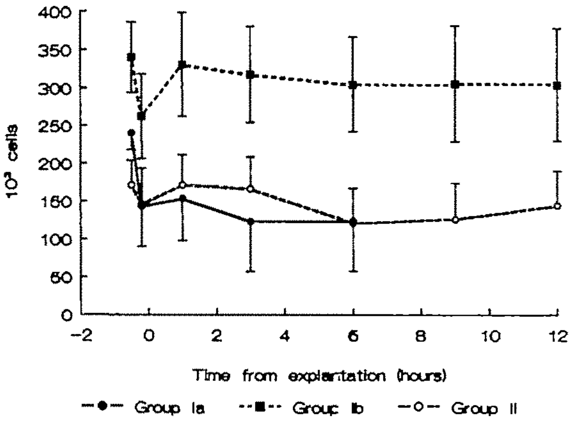

Fig 11. Platelet counts in study II autoperfused, working heart-lung preparations (group Ia, untreated short survivors; group Ib, untreated long survivors; group II, leukocyte depleted).

Imaging the organ blocks confirmed pulmonary leukosequestration in the autoperfused preparations. Preflush activity in the region of the lungs was slightly higher in the autoperfused preparations than in the controls, but this was not significant. Preflush activity in the region of the heart was quite different. Group I autoperfused preparations had significantly lower activity than group II (controls). These early differences are explained by sequestration of 80% of the granulocytes in the autoperfused preparation at 60 minutes of perfusion. A low level of activity in the region of the heart in the preflush autoperfused preparations is a reflection of the low activity in the circulating blood volume. The increased activity in the region of the heart in the group II controls occurs because granulocytes are not sequestered and are in the circulating blood volume. Flushing the organ blocks clears the circulating blood volume activity. Postflush scans demonstrate a greater than 80% retention of activity in the region of the lungs in group I autoperfused preparations with less than 50% retention of activity in group II controls. In each group the postflush retention of activity in the region of the heart was less than 25%, and it was similar in both groups. The scans thus document that leukosequestration in the pulmonary bed occurs early in the autoperfused working heart-lung preparation. The cellular counts confirm this finding.

In study II we looked at leukocyte depletion as a means of increasing the survival of the autoperfused preparations. Lung injury is a complex problem which incorporates cellular elements as well as chemical mediators [20]. Leukocytes have been extensively implicated in this process of acute lung injury [21]. Kontos and associates [11] have reported that leukocyte depletion ameliorates the pulmonary vasoconstrictor response seen in the autoperfused, working heart-lung preparation. Their study used a leukocyte filter in the autoperfused circuit, which has some inherent problems. Leukosequestration occurs very quickly, and undoubtingly cells are sequestered on the first pass through the lungs, which the filters would not address. Leukocyte filters also are not selective, and platelets are removed as well. We chose to deplete our animals of leukocytes with nitrogen mustard to avoid these problems. The leukocyte counts decreased to less than 10% of baseline, whereas platelets counts decreased but only to 54% of baseline, leaving a substantial circulating platelet mass.

Survival in the control group I produced a bimodal distribution with short survivors, group Ia, functioning for 8 hours whereas long survivors, group Ib, functioned for greater than 24 hours. This inconsistency in survival has been perceived as one of the major problems with autoperfusion as a method of preservation [22]. The leukocyte-depleted preparations, group II, eliminated this subset of short survivors. All were long survivors with a range of 20 to 32 hours. Mean survival in the rabbit autoperfused heart-lung preparation initially was reported as 4.36 hours [23]. Kaplan and colleagues [12] have reported mean survivals of 9.33 hours, and thus this report appears to have produced one of the longest average survival times for the rabbit autoperfused preparations.

The ex vivo working heart-lung preparation is a dynamic functioning organ block. It is simplistic in concept, a heart-lung block pumping oxygenated blood to a reservoir and returning. The autoregulatory mechanisms that maintain hemodynamic stability of the intact animal are no longer present, and thus one must artificially set the parameters. The venous return is adjusted by regulating the inflow, and the systemic resistance is adjusted by setting the height of the reservoir. We chose to set the inflow to establish an initial pulmonary artery pressure of 4 ± 0.5 mm Hg. Cardiac output as directly measured was variable with no difference between the groups. The low-flow state established was believed to be beneficial for the preparation. The metabolic demands of the heart-lung blocks are minimal, and low flows were believed to prevent volume overload of the pulmonary circuit. Kontos and associates [11] have demonstrated that a severe pulmonary vasoconstrictor response that is directly flow dependent occurs upon institution of the autoperfused preparations. Others have shown increased viability of preparations with reduced circulating blood flow [24]. Once established, the autoperfused preparation was placed in a humidified chamber at 25°C. Cardiac function was assessed by monitoring pulmonary artery pressure, left atrial pressure, and cardiac output throughout the duration of the preparation. Hemodynamic data were unable to distinguish the short versus long survivors. There was wide variability between preparations, and the only conclusion we could draw was that the pulmonary artery pressure rose over time in all groups as did the left atrial pressure. Interestingly the leukocyte-depleted group II showed no change in the left arterial pressure over the first 12 hours. The short survivors, group Ia, appear to have a more rapid rise in their pulmonary artery and left atrial pressure but this was not significant. Cardiac function generally appears to be well preserved throughout the life of the preparation until its demise. This is in agreement with the results obtained by others [8, 9, 12].

Pulmonary function as determined by pulmonary compliance and arterial blood gas analysis showed a mixed picture. Arterial blood gas analysis demonstrated adequate oxygenation over 12 hours. Conversely, pulmonary compliance demonstrated a steady decrease over time in all three groups. The lungs of the short survivors were initially more compliant, but this quickly changed as these preparations failed. This decrease in compliance is believed to be a manifestation of pulmonary injury (edema).

Eicosanoids have been implicated as a mediator for these changes in pulmonary compliance. Studies have shown that indomethacin pretreatment in the rabbit autoperfused heart-lung preparation decreases eicosanoid production and prevents the decrease in compliance seen in untreated preparations at 6 hours [12]. The eicosanoid thromboxane A_2 is a potent vasoconstrictor and platelet aggregator and is believed to play an important role in lung injury [25]. We have previously reported on the production of the eicosanoids in the rabbit autoperfused heart-lung preparation and have shown that institution of the preparation is a strong stimulus for their production [17]. The metabolites of prostacyclin increase dramatically as does the longer-lived metabolite of thromboxane A_2, 11-dehydrothromboxane B_2. The production of the stable metabolite 11-dehydrothromboxane B_2 appears to distinguish the long from the short survivors. In the short survivors the production increased dramatically over the first 6 hours of perfusion, whereas the long survivors has a slow, steady rise over time. The leukocyte-depleted preparations demonstrated a pattern similar to that of the long survivors.

Cellular elements have an important role in the production of eicosanoids. The primary cellular elements of interest are the platelets and the leukocytes. Platelets are a potent source of thromboxane A_2 yet demonstrated minimal change over time. Rabbits have a varied response to heparinization, and early changes seen in the platelet counts primarily reflect this finding [26]. Leukocytes, on the other hand, show no early changes in regard to heparinization but show a dramatic change upon the institution of the autoperfused preparation. We have reported in a previous study that there is initially a proportional sequestration of lymphocytes and granulocytes. As perfusion continues, this becomes predominantly a sequestration of granulocytes [17]. The leukosequestration occurs in all the preparations, including the leukocyte-depleted group but to less of a degree. The cause of this sequestration is not fully understood, but several theories exist. It has been demonstrated in a canine model that decreased cardiac output and consequently decreased pulmonary blood flow leads to pulmonary sequestration of leukocytes [27]. Our autoperfused preparation incorporates such a low-flow state. The autoperfused preparation also incorporates a reservoir and tubing, which are well-known stimuli for the activation of complement in the blood [28, 29]. Directly measured levels of complement-derived peptides C5a and C3a have been shown to increase after cannulation and institution of a calf autoperfused working heart-lung preparation [30]. These peptides are well-known chemotactic and leukocyte aggregating peptides [31]. Multiple organ block autoperfusion preparations, however, do not incorporate a reservoir and still manifest a dramatic decline in the circulating leukocytes upon institution of the preparations [32]. Another factor in the puzzle of leukosequestration involves the eicosanoids. Leukotrienes, the products of the lipoxygenase metabolic pathway of arachidonic acid, are well known to be chemotactic for granulocytes [33].

A new component in this puzzle of leukosequestration is the family of adhesion-receptor glycoproteins designated the selectins. These selectins are expressed on the surfaces of platelets and leukocytes, as well as endothelial cells. The homing receptor selectin LECAM-1 is expressed on leukocytes and facilitates their binding to endothelium. The ELAM-1 glycoprotein is synthesized by endothelial cells in response to a variety of inflammatory stimuli and promotes adhesion of granulocytes, monocytes, and lymphocytes [34]. Future adhesion inhibitors may play a major role in preventing this leukosequestration. The stimuli leading to pulmonary leukosequestration in the autoperfused preparation are not fully understood and most likely are multifactorial.

Conclusions

Leukocyte sequestration is an integral part of many forms of acute lung injury. The sequestration of leukocytes is one of the first events to occur upon institution of the autoperfused working heart-lung preparation and perhaps is equivalent to the sequestration of granulocytes in patients who manifest one of the most severe forms of lung injury, the clinical syndrome of adult respiratory distress syndrome [35]. Instituting the autoperfused preparation triggers leukosequestration and sets up a cascade of events that lead to acute pulmonary injury and ultimately its own failure. Understanding this cascade of events could enable us to better preserve organ blocks for transplantation. Understanding this process of pulmonary injury is a complex problem of which leukocytes surely are a prime player, though obviously not the sole player. In conclusion, pulmonary leukosequestration of granulocytes occurs early in the autoperfused working heart-lung preparation, and leukocyte depletion stabilizes the autoperfused working heart-lung preparation by eliminating the subset group Ia short survivors.

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DISCUSSION

DR JOEL D. COOPER (St. Louis, MO): The inconsistency between the two groups, you say, could be sorted out by the amount of prostanoids produced after the beginning of the working of the model?

DR GENCO: In study II, the variable that distinguished long versus short survivors in the control group was the production of the prostanoid thromboxane.

DR COOPER: And as far as white blood cell counts, platelets, everything else was the same?

DR GENCO: Yes. White blood cell counts decreased in all preparations as these cells are sequestered. Platelet counts also decreased but to varying degrees. The significant decline in platelet count primarily occurred after heparinization if it occurred at all.

DR COOPER: How long is the model good for under ordinary circumstances?

DR GENCO: Initial work with the rabbit autoperfused, working heart-lung preparation had on the order of 4 to 7 hours of organ block survival. Our work over the last several years has enabled us to consistently obtain survivals of greater than 24 hours.

DR THOMAS M. EGAN (Chapel Hill, NC): I enjoyed your report, and I have just one question. How many animals died as a result of getting nitrogen mustard?

DR GENCO: In actuality no animals died as a result of nitrogen mustard treatment.

DR EGAN: The reason I asked was just to pose the question, could it be that you are preselecting out the lungs, because my recollection of giving nitrogen mustard to laboratory animals is that they look like the wrath of God after three days.

DR COOPER: These were sheep, as I remember.

DR EGAN: No, we used it in rabbits as well.

DR COOPER: Okay. Because we actually have used a dose in rabbits recently and found excellent depletion of white blood cells without the same sort of problems that we had at one time in sheep.

I think a lot of discussion today has grouped together ischemia and reperfusion as if it is one item. I must tell you that I increasingly think that there are two totally different phases and that the nature of the injury during ischemia very much determines the nature of what is going to happen during reperfusion. I think that if you avoid an ischemic injury, then all of these methods, whether superoxide dismutase or verapamil or leukocyte depletion, may in fact not be so relevant. So that is why I asked about how long your model was good for. I think part of the inconsistency in some of the results we see, the benefits or the nonbenefits of leukocyte depletion, may be related to the nature of the injury that is occurring during the ischemic or so-called ischemic period.

DR GENCO: We agree. Early events upon institution of the autoperfused, working heart-lung preparation more than likely determine its fate. Early sequestration of white blood cells probably plays a major role in the ultimate failure of the preparations. This sequestration of cells along with the release of mediators probably occurs in other methods of heart lung preservation (core cooling and cold flush techniques), and these events probably play a major role in organ injury seen during preservation.

DR TIMOTHY S. HALL (Baltimore, MD): Dr George Kontos recreated much of the working heart-lung research that Dr Robicsek started years ago. He used a leukocyte depletion preparation as well, showing the same type of results as presented here. To answer your earlier question, he was able to show reproducible and stable preparations for prolonged periods using leukocyte depletion, isoproterenol (for beta effects), and substrate enhancement.

An interesting point your work emphasizes is the release of vasoactive mediators from this preparation. This may represent a type of active injury model because of ongoing mediator release.

Advances in Aortic Arch Surgery

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From 1980 to January 1991, 130 patients (89 men and 41 women, aged 22 to 76 years; mean age, 52 years) underwent 133 interventions on the aortic arch. Aneurysm was diagnosed in 57 patients, whereas 29 had chronic and 44 acute aortic dissection. In 67 instances a partial and in 35 instances a total arch replacement was performed. The distal arch was approached through a left thoracotomy in 14 patients. Local interventions (n = 17) included surgical reconstruction and glue procedures. Additionally, 55 patients required aortic valve replacement, preferably with composite grafts (n = 46), whereas the valve was reconstructed in 14. Procedures were performed using hypothermia (nasopharyngeal temperature, 11° to 25°C) and circulatory arrest (mean time, 27 minutes). Early mortality was 13.9% at the first operation on the aortic arch. Early deaths included 7 of 57 patients with aortic aneurysm (12.3%), 2 of 29 patients with chronic dissection (6.9%), and 9 of 44 patients with acute dissection (20.5%). Neurological (n = 6) and cardiac events (n = 5) were the most common causes of early death. Since 1987, 7 of 88 patients have died for an overall mortality of 8.0%. With growing experience, proper indication, and adequate operative strategy including the use of circulatory arrest in hypothermia, operation on the aortic arch can be performed with an acceptable risk.

(Ann Thorac Surg 1992;53:227–32)

Aneurysms and dissections of the transverse arch continue to present a surgical challenge because several obstacles have to be overcome to obtain satisfactory results [1, 2]. First, the brain must be protected against cerebral ischemia during interruption of blood flow in the brachiocephalic vessels. Second, the heart must be protected during clamping of the ascending aorta. Circulatory arrest in moderate or deep hypothermia provided by extracorporeal circulation as suggested by Borst and co-workers [3] and introduced into arch repair in aneurysm and dissection by Griepp and co-workers [4] and Crawford and co-workers [5] might be an answer for both. This study covers our experience with this method with special respect to the techniques of extracorporeal circulation, the repair of arch and aortic valve in acute and chronic dissection, and the postoperative outcome with attention to neurological complications.

Patients and Methods

From 1980 to January 1991, 130 patients underwent 133 procedures on the aortic arch. Table 1 gives the numbers, sex distribution, and age of patients with respect to the underlying pathology. Forty-five percent of the patients had aneurysms, whereas 34% and 22% had acute or chronic dissection, respectively (Table 1). One hundred nineteen procedures were performed through a median sternotomy, whereas in 14 patients with distal arch disease the access was through a left thoracotomy (Table 2).

Moderate to deep hypothermia was provided by extracorporeal circulation. Patients were cooled down to a nasopharyngeal temperature of 11° to 25°C (mean, 18°C). The period of circulatory arrest averaged 27 minutes, ranging from 10 to 64 minutes. For additional cerebral protection the patients received a 5 $mg \cdot kg^{-1} \cdot h^{-1}$ sodium pentobarbital infusion starting with anesthesia. Furthermore, the head was packed in ice bags.

With a transsternal approach, venous drainage was through a single cannula in the right atrium. With left thoracotomy the right ventricle was intubated retrogradely through the pulmonary artery trunk with a rectangular cannula (36F). In these cases no cardioplegic solution was applied. In patients with the transsternal approach, cardiac protection routinely was achieved by crystalloid cardioplegia and irrigation of the pericardium with cold saline solution.

In most instances one of the femoral arteries was used as arterial inflow. In 7 of the patients with dissection a drop in the right radial versus femoral artery pressure indicated malperfusion of the supraaortic branches due to retrograde perfusion. This was reversed by cannulating the ascending aorta directly in 4 patients and through the left ventricular apex in 1 patient with a second arterial line which we usually have on the operating table in dissection. In 2 patients the dissecting membrane was fenestrated within the aortic arch during a short preliminary circulatory arrest.

Recently, in patients with aneurysm and chronic dissection we have intubated the proximal aorta at a site that has reasonable quality of aortic wall and is obviously nondissected. For rewarming the aortic arch prosthesis is

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Table 1. Patient Characteristics

Pathology	No. of Patients	Sex (M/F)	Age (y)
Aneurysm	57	36/21	55 ± 14
Chronic dissection	29	20/9	50 ± 10
Acute dissection	44	33/11	51 ± 15
Total	130	89/41	52 ± 13[a]

[a] Range, 25 to 76 years.

intubated. In this way only one arterial cannula is necessary, which provides antegrade flow throughout the procedure. Antegrade flow during reperfusion is recommended in dissection and, of course, is mandatory in all patients having undergone the elephant trunk procedure [6]. Intubation of the aortic arch prosthesis is performed directly through a stab incision rather than through a side tube (Fig 1C).

The aortic valve could be retained or repaired in 60% of acute dissections (Table 3). Recently, we have started to reconstruct the aortic root and proximal arch using resorcin formol glue (Gelatine Resorcin Formol Glue; Cardial, St. Etienne, France). The true lumen of the aortic root as well as that of the arch is stuffed with a sponge, thereby remodeling the anatomical sizes of both structures (Figs 1A, B). After this, the sickle-shaped false lumen is filled with the glue mass, which firmly readapts the layers, at the same time producing a leatherlike aortic wall [7, 8]. Using this technique we also repaired aortic insufficiency due to chronic dissection in 2 patients. The proximal orifice of the ascending aortic prosthesis served as a frame which keeps the aortic valve commissures in their normal anatomical position. Figure 2A is a preoperative example of an acute dissection, DeBakey type I, which was converted into a DeBakey type III dissection by replacement of the ascending aorta after reconstruction of aortic root and arch using glue (Figs 2B, C). In 37 patients with aortic insufficiency due to annuloaortic ectasia the aortic valve was replaced, usually with composite grafts.

Results

Early mortality including all patient categories was 13.9% (Table 4). Up to 1986 it was 26%. Since 1987 7 of 88 patients had died, representing an early risk of 8.0%. Five of the recent deaths occurred in patients with acute dissection or ruptured aneurysm operated on emergently. Major causes of death (Table 5) were cardiac and cerebral complications. Other fatalities were due to hemorrhage, sepsis, multiorgan failure, and distal aortic rupture.

Among nonlethal complications we observed hemiplegia in 3 patients with complete restoration in 1 and partial recovery in another. Two patients experienced paraplegia, which was partially reversible in 1; in the other patient paraplegia had developed preoperatively and persisted after operation.

In the 112 patients surviving the first hospitalization, 24 reoperations were performed in 16 patients, corresponding to a reoperation rate of 14.3%. Figure 3 summarizes the location of reoperations. Predominant locations were the descending thoracic and thoracoabdominal aortic segments.

We observed 11 late deaths (9.8%). Table 6 recapitulates the causes of late death. Only four of the late deaths could be related to the aortic disease. Mean follow-up of the early survivors was 32.2 months, ranging from 2 to 123 months. Two patients were lost to follow-up; 41 were formally restudied by angiography and computed tomography. Figure 4 demonstrates the actuarial survival (Cutler-Ederer) with respect to aortic disease. Overall actuarial survival at 1 year was 84.5%; at 5 years it was 69.1%.

Comment

Without treatment the life expectancy in patients with aneurysm and dissection is limited, the literature referring to a 5-year mortality of 57% in the spontaneous course of chronic dissection and aneurysm [9–11]. For acute aortic dissection the pressing indication for operation due to the extreme mortality after onset of the disease has been described by Anagnastopolos and associates [12] and Daily and co-workers [13]. The reduction of early mortality in operation on the aortic arch down to a level of 10% and below allows a more liberal decision for surgical intervention. In type A acute aortic dissection, we have abandoned reconstructive measures of the proximal arch using Teflon felt. Instead we now tend to glue the dissecting layers of the arch with resorcin formol glue and perform an open anastomosis afterwards [14]. Using this approach, the development of aneurysm/ectasia of the junction between ascending aorta and arch can be pre-

Table 2. Operative Procedures Performed During Repair of Aortic Arch in 130 Patients

Pathology	Reconstruction, Glue Procedures	Proximal Arch Replacement	Total Arch Replacement[a]	Distal Arch Replacement
Aneurysm (n = 58)	8	24	16	12
Chronic dissection (n = 31)	2	16	10	2
Acute dissection (n = 44)	7	27	9	0
Total (n = 133)	17	67	35	14

[a] Includes cases of additional implantation of elephant trunk prosthesis into descending thoracic aorta.

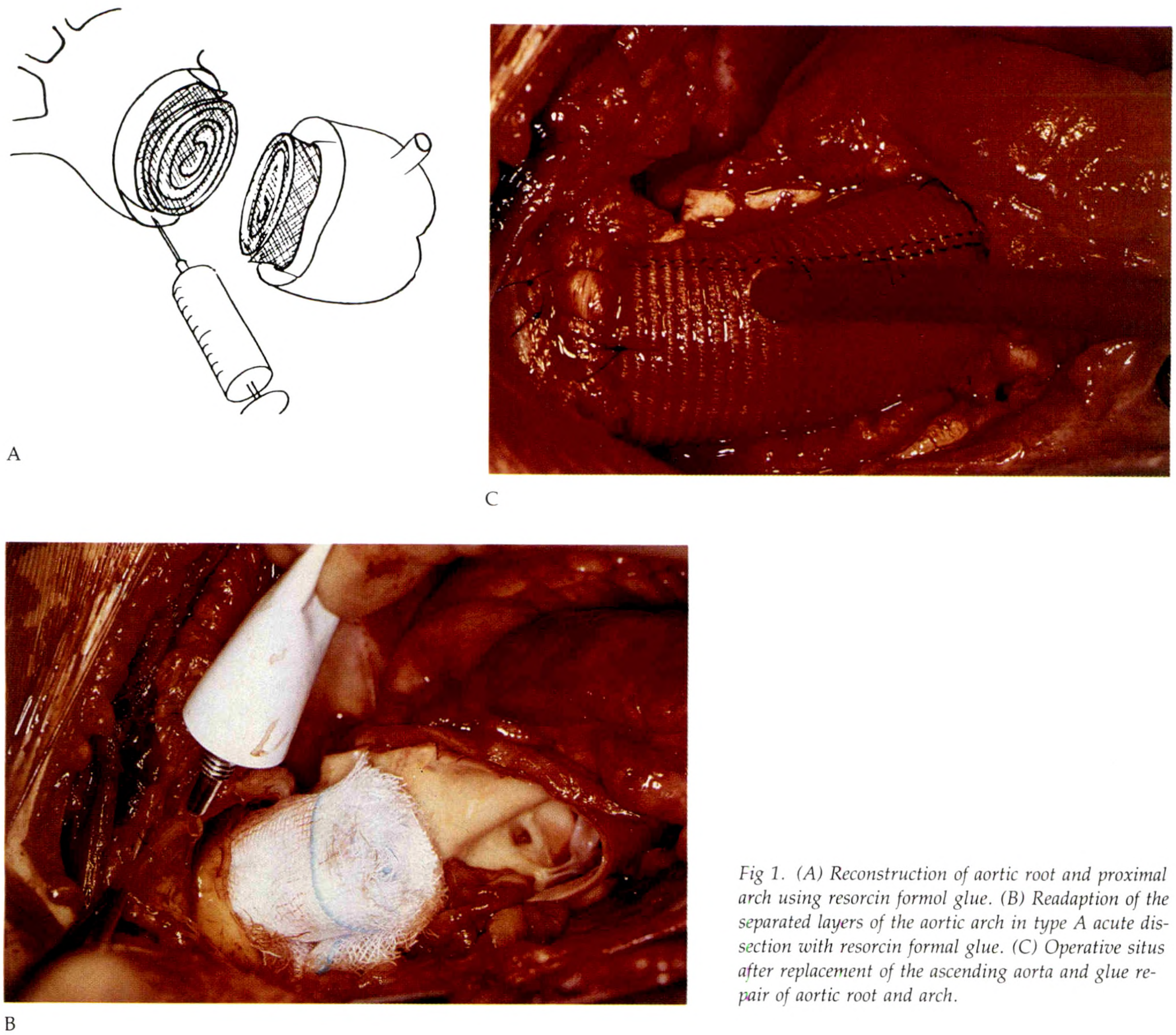

Fig 1. (A) Reconstruction of aortic root and proximal arch using resorcin formol glue. (B) Readaption of the separated layers of the aortic arch in type A acute dissection with resorcin formal glue. (C) Operative situs after replacement of the ascending aorta and glue repair of aortic root and arch.

vented without increasing the operative risk, as we showed recently [15, 16]. Preliminary follow-up studies with digital subtraction angiography and computed tomographic scan indicate that the glued arch and the aortic root do not tend to dilate. One patient with previous arch gluing was reoperated on recently for dilatation of the proximal descending thoracic aorta. Intraoperatively, the arch was found to be nondissected and its wall of leatherlike quality.

Table 3. Procedures on the Aortic Valve

Pathology	No Valve Procedure	Valve Repair	Valve Replacement
Aneurysm (n = 58)	34	0	24
Chronic dissection (n = 31)	15	3	13
Acute dissection (n = 44)	15	11	18
Total (n = 133)	64	14	55

Due to our improved results, we also more liberally apply the elephant trunk method for aortic arch replacement, which positively simplifies the following replacement of the descending thoracic aorta during a second-stage procedure [6].

In acute and chronic dissection the reverse blood flow during extracorporeal circulation with one of the femoral arteries serving as arterial inflow may lead to an obstruction of vital aortic branches of any location [17] by a blind pocket phenomenon. The supraaortic branches here rank first. Therefore, we recommend a multilocal control of the arterial perfusion pressure (right and left radial artery, right femoral artery) for intimate recognition of malperfusion. This can be reversed by restitution of antegrade flow, which can be achieved by cannulation of the ascending aorta either directly or through the left ventricular apex. Thus, we recommend to routinely have a second

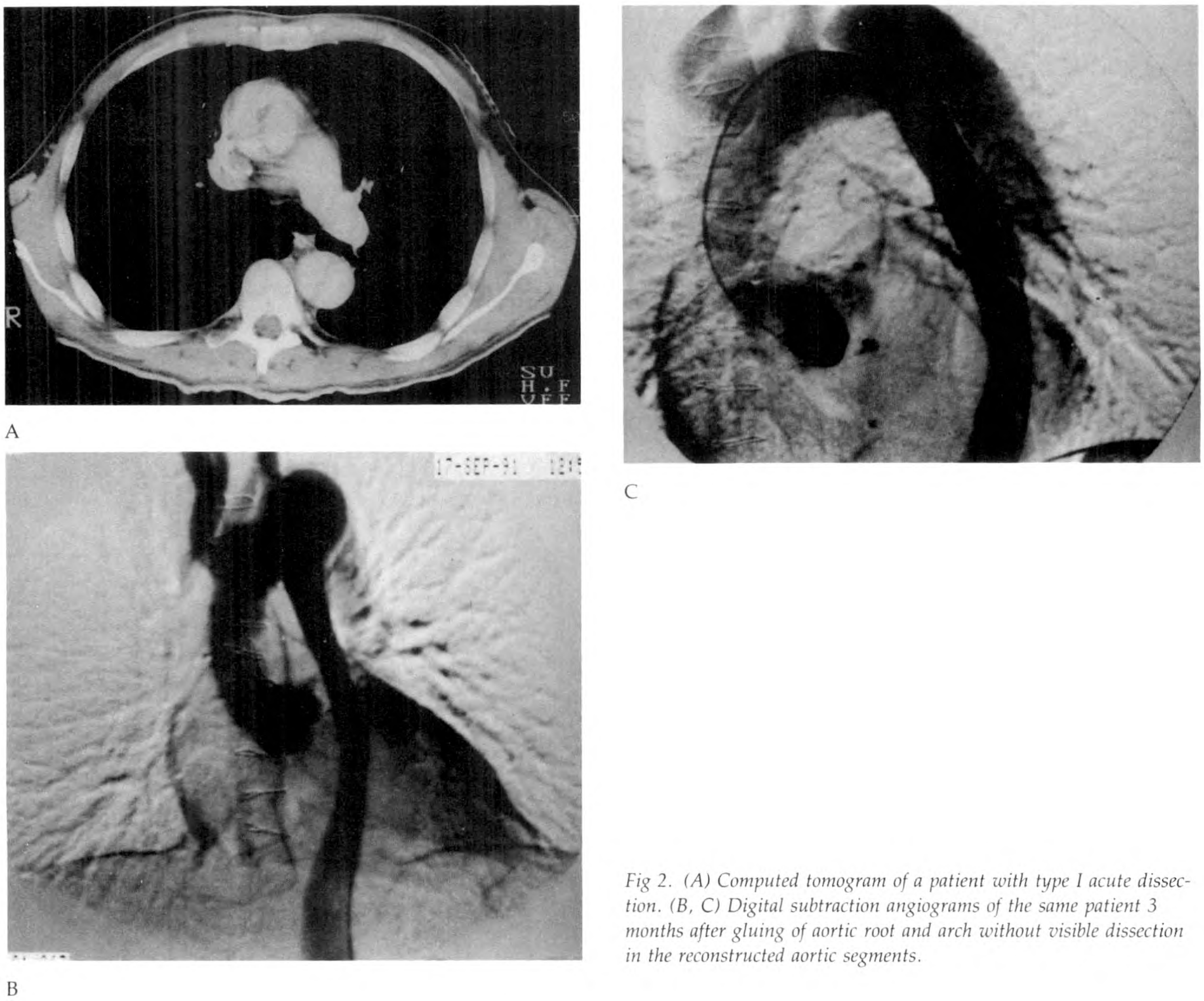

Fig 2. (A) Computed tomogram of a patient with type I acute dissection. (B, C) Digital subtraction angiograms of the same patient 3 months after gluing of aortic root and arch without visible dissection in the reconstructed aortic segments.

arterial line ready when operating on this kind of disease. In one instance we were able to reverse the blind pocket phenomenon by fenestration of the dissection membrane in the aortic arch during a short period of circulatory arrest.

Table 4. Hospital Mortality for First Operation on Aortic Arch Versus Underlying Pathology From 1978 to 1986 and From 1986 to January 1991

	1978–1986		1987–Jan 1991	
Pathology	n	%	n	%
Aneurysm (n = 57)	4/21	19	3/36	8
Chronic dissection (n = 29)	2/10	20	0/19	0
Acute dissection (n = 44)	5/11	45	4/33	12
Total (n = 130)	11/42	26	7/88	8

For reperfusion after arch repair we prefer antegrade perfusion in dissection. Antegrade perfusion, of course, is mandatory in patients operated on with the elephant trunk method.

Replacement of the aortic valve with a biological or

Table 5. Causes of Early Mortality After First Operation on Aortic Arch

Pathology	Cardiac	CNS	Other
Aneurysm (n = 57)	3	4	0
Chronic dissection (n = 29)	0	1	1
Acute dissection (n = 44)	2	1	6
Total (n = 130)	5	6	7

CNS = central nervous system.

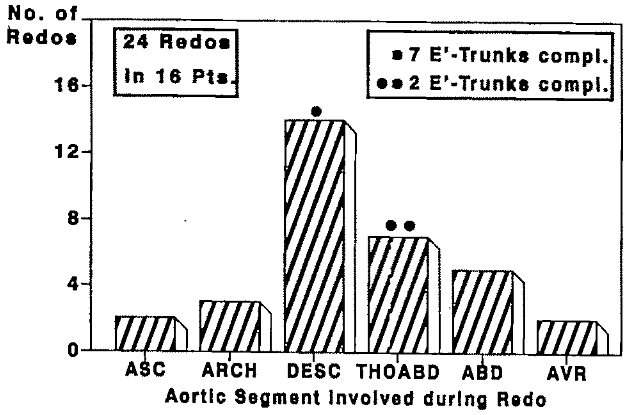

Fig 3. Location of reoperation after repair of the aortic arch. (ARCH = *aortic arch;* ASC/DESC/THOABD/ABD = *ascending/descending/thoracoabdominal aortic segment;* AVR = *aortic valve replacement.)*

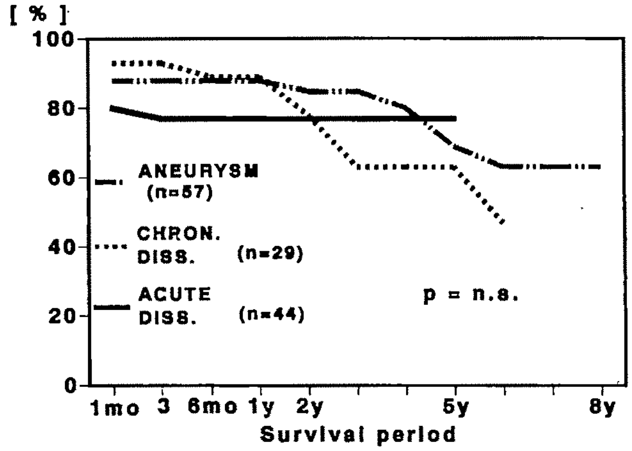

Fig 4. Actuarial survival after arch operation versus pathology. (Diss. = *dissection;* n.s. = *not significant.)*

homologous substitute implies the risk of degeneration, whereas the use of a mechanical valve entails the risk of thrombembolism and bleeding. Preservation of the native valve could eliminate these risks. However, with reconstruction of the aortic root using Teflon felt, a substantial portion of the aortic bulbus remains and might undergo dilation with the risk of rupture or development of annuloectatic aortic insufficiency. When reconstructing the aortic root with resorcin formol glue, the suture line of the anastomosis with the ascending aortic graft can be positioned much closer to the aortic annulus than with the conventional method. Thus a substantially greater portion of the aortic root can be excluded. Preliminary follow-up controls up to 18 months so far do not show secondary root dilatation. Furthermore, it has to be pointed out that reconstruction of the aortic valve is possible in chronic dissection when the true lumen of the ascending aorta is of normal caliber. The proximal orifice of the ascending aortic prosthesis thereby serves as a frame keeping the commissures in proper position.

The high incidence of aortic reoperation and the low incidence of late mortality due to aortic disease demonstrates that an aggressive surgical approach combined with a close follow-up can markedly improve the prognosis of patients with dissection or aneurysm of the aortic arch.

Table 6. Causes of Late Mortality

Pathology	Cardiac	Aortic Rupture	Died After Redo	Other/ Unknown	Total
Aneurysm	2	2	0	1	5
Chronic dissection	1	0	2	3	6
Acute dissection	0	0	0	0	0

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DISCUSSION

DR DELOS M. COSGROVE III (Cleveland, OH): Let me just ask you a question so that you might clarify it a little bit for us, some of those who do not have the hexylresorcinol glue. You paint the tissue with the hexylresorcinol glue. You use no Teflon felt and you simply sew the graft to the treated tissue. Is that correct?

DR LAAS: Using the glue, we so far have not had to use any Teflon felt at all. In one of the recent cases with type I dissection and extensive gluing of the layers in the arch portion we did not find any dissection of the downstream aorta in the postoperative angiogram.

DR COSGROVE: This is clearly a major advance in the treatment of this type of disease. Do any other of our European colleagues have experiences that they would like to share with us? Is this available in Canada?

DR LAAS: One more piece of advice for use of the glue. The second component is formol, which is toxic. Thus, we stuff a sponge into the true lumen with the orifices of coronary arteries in the aortic root or the supraaortic branches in the arch portion. In this way the toxic agent is prevented from getting into the circulation.

DR GRAEME L. HAMMOND (New Haven, CT): How do you keep the glue inside the false lumen when you have a large, stellate tear above the coronary arteries?

DR LAAS: If the intimal cylinder of the right coronary ostium is intact one can use the glue routinely. In case of a tear in this portion we would be reluctant to use the glue.

DR HAMMOND: Do you protect the coronary arteries when you are placing the glue?

DR LAAS: Yes, as pointed out in our presentation a sponge is inserted into the aortic root to prevent the glue from flowing into the coronary ostia.

Blunt Injuries of the Thoracic Aorta

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We managed 51 patients with thoracic aortic injuries caused by blunt trauma between 1977 and 1990. Forty-nine injuries were located in the upper descending aorta and one each in the ascending aorta and aortic arch. Three patients arrived moribund and underwent thoracotomy for resuscitation, and all died. The diagnosis was confirmed by aortography in 48. One patient died of aortic rupture, 1 died of hypoxemia, and 1 refused operation and died. Forty-four patients had aortic repair, 42 with graft insertion. Gott shunts were placed in 23 with 3 cases of paraplegia (13%). Simple cross-clamping was used in 19 with 1 case of paraplegia (5.2%). We found statistically significant differences between the cross-clamp times of patients without paraplegia compared with those in whom paraplegia developed in both the shunt and no-shunt groups. Logistic regression analysis showed that the only factor significantly associated with paraplegia was cross-clamp time. There were two postoperative deaths (4.4%). Seven patients had medical therapy initially and aortic repair was delayed to allow other injuries to stabilize. Before aortic repair, 18 patients had intraarterial pressure monitoring and 34 received β-blockers or antihypertensive drugs. We conclude that aortic repair with graft insertion is usually successful in nonmoribund patients, simple cross-clamping is associated with a relatively low risk of paraplegia, the incidence of paraplegia is directly associated with the duration of cross-clamp time, and selected patients can be managed medically while awaiting aortic repair.

(Ann Thorac Surg 1992;53:233–9)

Blunt traumatic disruption of the thoracic aorta remains a highly lethal injury. It appears that only preventive measures that may reduce the frequency of this injury could have any effect on the mortality in the prehospital phase [1]. Only the patients who reach the hospital with the false aneurysm intact and a blood pressure and cardiac rhythm present have a chance of survival. In these patients mortality and morbidity may arise from the multiple severe associated injuries, from delay in recognition of the aortic injury, from sudden rupture of the false aneurysm during angiography and transportation to the operating room, and from complications of aortic repair such as hemorrhage, paraplegia, and renal failure. Controversial issues involve diagnostic studies, timing of aortic operation, method of aortic repair, and spinal cord protection during aortic clamping [2–7].

We reviewed our experience with all patients treated at the Massachusetts General Hospital with acute blunt traumatic disruption of the thoracic aorta from January 1977 to June 1990. This time period was selected because 1977 marked the end of the use of systemic heparinization and partial cardiopulmonary bypass for descending aorta repairs. Experience from our institution between 1970 and 1980 has been previously reported [7]. In that study we found that the mortality rate for aortic repair was substantially higher in patients treated with heparinization and bypass than in those who were shunted and received no heparin. Hemorrhage was the major cause of death in the bypass group. We also noted that aortic repair could be safely delayed in selected patients who were managed medically while other severe injuries were stabilized.

Material and Methods

The medical records of all patients with acute blunt traumatic disruption of the thoracic aorta were reviewed. Particular attention was directed to the emergency ward record, the operative and anesthetic reports, the postoperative course, and autopsy reports. Statistical analysis included comparison of paraplegia rates by the Fisher exact test, cross-clamp times by unpaired t tests and one way analysis of variance, and factors associated with paraplegia by multivariate logistic regression analysis.

Clinical Material

Between 1977 and 1990 we treated 51 patients with acute blunt injuries to the thoracic aorta. There were 43 male and 8 female patients whose average age was 35 years, with an age range of 16 to 70 years. Circumstances of the accidents were as follows: drivers of motor vehicles, 33; passengers in motor vehicles, 8; pedestrians struck by autos, 4; motorcycle riders, 4; and victims of falls, 2. Information regarding seat belt use and ejection of the victim from the vehicle was not available in sufficient numbers to draw any conclusions about these factors.

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Four patients came directly to our hospital, and 47 patients were referred from other institutions.

Initial arterial blood pressures were unobtainable in 3 patients and less than 100 mm Hg systolic in an additional 7 patients. Initial systolic arterial pressures were greater than 140 mm Hg in 22 patients. Decreased femoral pulses were noted in 8 patients. A visible or palpable chest wall injury was apparent in only 20 patients (39%). Four patients had a flail chest. Seven patients had an audible murmur, and in 2 of these it was probably due to preexisting heart disease.

Reports of chest radiographs were available for review in 48 patients, and all of them showed superior mediastinal widening, although in 3 patients the widening was not present on the initial films. Other common findings were obscuring of the aortic knob contour in 10, an extrapleural apical cap in 7, lateral shift of mediastinal structures in 13, lung contusion in 20, rib fractures in 20, pleural effusions in 20, and pneumothorax in 10. Nine patients had computed tomographic scans of the chest, and in only 4 were findings suggestive of aortic injury. Three were read as probable aortic injury, one as descending aortic dissection, and the other five showed only mediastinal hematomas and pleural effusions.

Associated injuries were common and severe, and included head injuries, intrathoracic organ damage, abdominal injuries, fractures, and peripheral vascular and nerve injuries. Details of the associated injuries are summarized in Table 1.

Table 1. Associated Injuries

Injury	No. of Patients
Head injuries	
Concussion	15
Cerebral hematomas requiring operation	5
Thoracic injuries	
Cardiac contusion	4
Lung contusion	20
Right atrial rupture	1
Tracheal laceration	1
Left diaphragm rupture	1
Abdominal injuries	
Liver laceration	6
Ruptured spleen	5
Retroperitoneal hematoma	6
Fractures	
Ribs	20
Sternum	1
Clavicle	4
Facial bones	8
Spine	5
Upper extremity	11
Lower extremity	25
Pelvis	13
Vascular injuries	
Femoral artery	2
Peripheral nerve palsies	8

In 48 patients the diagnosis of aortic injury was confirmed by aortography, and in 3 moribund patients the aortic injury was found during emergency resuscitative thoracotomy. Forty-nine injuries were located in the upper descending aorta, one in the ascending aorta, and one in the aortic arch with involvement of the innominate and left common carotid arteries.

Our recent policy is to insert radial artery catheters for continuous pressure monitoring in patients strongly suspected of aortic injury, and to treat hypertension if present. Eighteen patients had arterial lines inserted in the emergency ward. Throughout the period of this study, we have commonly administered intravenous propranolol to patients who are not hypotensive and nitroprusside infusions to those who are hypertensive during their evaluation. A total of 34 patients received β-blocking drugs or vasodilators or both before their aortic repairs.

Surgical Procedures

Three patients arrived in our emergency ward without pulse or blood pressure and underwent resuscitative thoracotomy, and all 3 died. One patient arrested during transport from the angiography suite to the operating room and had a thoracotomy and aortic clamping, but he could not be resuscitated. Death was due to rupture of the false aneurysm. One patient died of hypoxemia and did not have an aortic repair. One patient refused operation and died (his auto accident was probably a suicide). One patient received long-term medical therapy because of paraplegia resulting from a thoracic spine fracture with direct spinal cord damage. The remaining 44 patients had aortic repairs: 42 with descending aortic injuries and 1 each with injury to the ascending aorta and the aortic arch. Thirty-three patients underwent immediate aortic repair. In 6 patients aortic repair was delayed 4 days to 4 months to allow stabilization of other severe injuries while medical treatment was administered to reduce the risk of aortic rupture. Five of the 6 patients had severe neurological injuries that were responsible for the delays, and 1 patient had a severe pulmonary contusion. In 4 patients the diagnosis of aortic injury was not made until 2 to 5 days after the accident, and aortic repair was accomplished immediately after their arrival in our hospital. One patient had a delayed diagnosis of aortic injury and his repair was delayed while electrocardiographic changes were evaluated. Therefore, aortic repair was performed immediately after confirmation of the diagnosis of aortic injury in 84% of the patients.

The ascending aortic injury was repaired through a median sternotomy on cardiopulmonary bypass with graft insertion. The aortic arch injury was repaired through a median sternotomy without bypass. A graft was placed from the ascending aorta to the innominate artery; a side arm graft was then placed to the left common carotid artery using electroencephalographic monitoring, and the aortic arch disruption was closed directly (Fig 1).

The descending aortic injuries were all exposed through

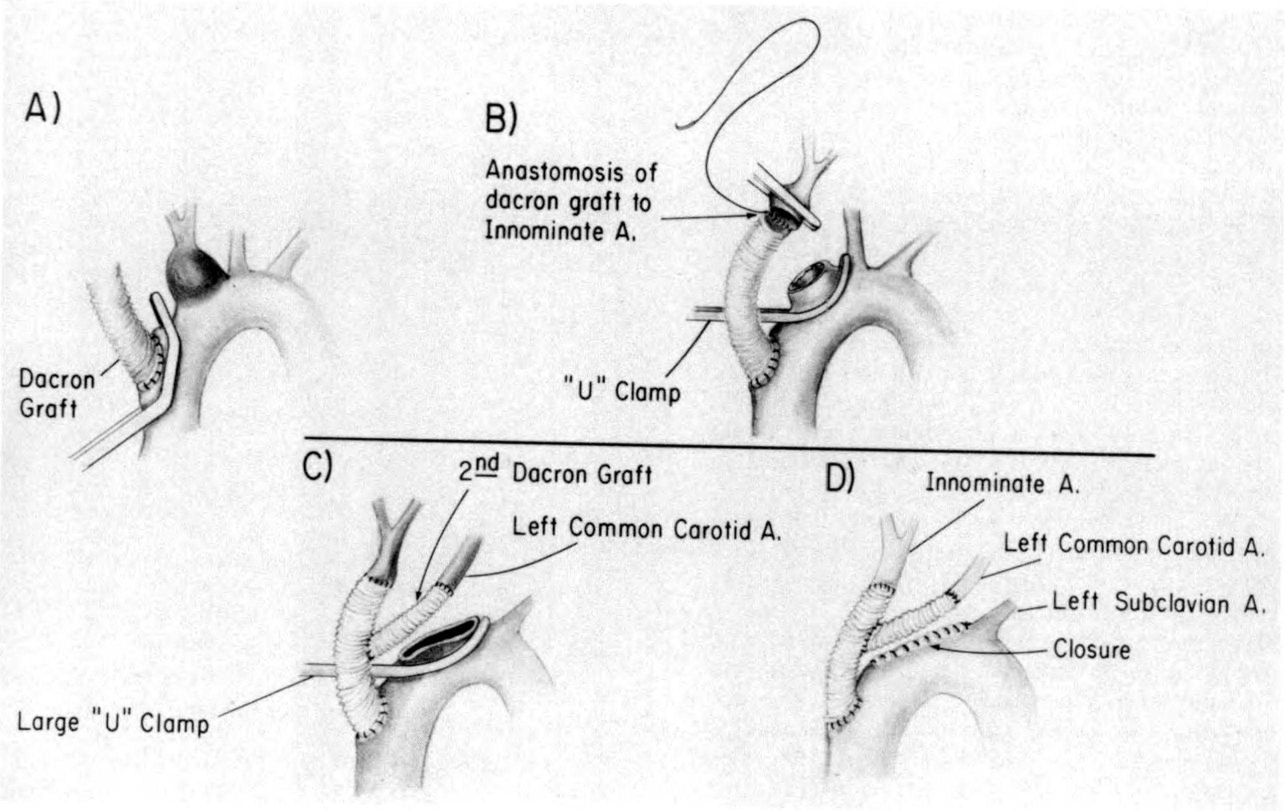

Fig 1. (A) Initial step in the repair of a false aneurysm of the aortic arch involving the innominate artery origin. An 8-mm Dacron graft is anastomosed to the ascending aorta. (B) Using electroencephalographic monitoring, the proximal and distal ends of the innominate artery are clamped and the distal anastomosis of the graft to the innominate artery is constructed. Inspection of the aortic arch showed extension of the intimal injury beyond the clamp into the origin of the left common carotid artery. Therefore a second Dacron graft, 6 mm in diameter, is anastomosed to the innominate artery graft as a side-arm before release of the clamps. (C) With the innominate artery perfused, the left common carotid artery is clamped and a larger clamp applied to the aortic arch. The distal anastomosis of the side-arm graft to the left common artery is completed. (D) To complete the repair, the aortic arch is closed directly, obliterating the intimal injury at the origins of the innominate and left common carotid arteries.

a left posterolateral thoracotomy with one-lung ventilation through a double-lumen endotracheal tube. The proximal clamp was applied between the left common carotid and left subclavian arteries in all cases. Simple cross-clamping was used in 19 patients and Gott shunts in 23. Shunt insertion sites are shown in Table 2. Dacron grafts were placed in all except 2 patients whose injuries were small and were sutured directly.

Operation for associated injuries was frequently required. Five patients underwent intracranial procedures before aortic repair. Concomitant intrathoracic procedures included suture of tracheal laceration, closure of right atrial rupture, and repair of ruptured diaphragm. Fifteen patients had laparotomies, five of which were performed before aortic repair. Open fracture reduction was performed in 28 patients, three of these before aortic repair.

Table 2. Gott Shunt Insertion Sites in 23 Patients

Site	No. of Patients
Proximal	
Ascending aorta	15
Aortic arch	4
Left ventricular apex	4
Distal	
Descending aorta	17
Left femoral artery	6

One patient required reexploration for bleeding. Vascular repair was necessary in 2 patients after shunt removal; 1 had a vein patch graft repair of a femoral artery, and 1 needed multiple repair sutures in the left ventricular apex. Five patients had tracheostomies.

Persistent postoperative hypertension was extremely common. A total of 39 patients received antihypertensive agents after hospital discharge. Only 3 patients discharged after aortic repair did not require drug therapy for hypertension.

Results

The overall mortality was 8 of 51 patients (15.7%), which includes those who died before an attempt at aortic repair.

There were two postoperative deaths in the aortic repair group of 44 patients (4.5% mortality). The deaths, one each in the shunt and no-shunt groups, were due to respiratory failure, sepsis, and renal failure. The average age of these 2 patients was 68 years, and both were female.

Paraplegia developed in 4 patients out of a total of 42 at risk (9.5%). The paraplegia rate was 1 of 19 in the no-shunt group (5.2%) and 3 of 23 in the Gott shunt group (13.0%). The difference in paraplegia rates was not statistically significant ($p = 0.6$ using the Fisher exact test). Aortic cross-clamp times were: no shunt, no paraplegia, 32 minutes; no shunt, paraplegia, 50 minutes; Gott shunt, no paraplegia, 45 minutes; Gott shunt, paraplegia, 80 minutes. One-way analysis of variance established differences among these groups. Unpaired t tests found significant differences between the cross-clamp times in the patients without paraplegia compared with those in whom paraplegia developed in both the shunt and no-shunt groups ($p = 0.02$ in the no-shunt group and $p = 0.0005$ in the Gott shunt group).

Using multivariate logistic regression analysis, we evaluated 19 factors for their association with the occurrence of paraplegia. Variables included presence of a shunt, cross-clamp time, hypotension, nitroprusside administration during aortic clamping, and administration of drugs such as mannitol, steroids, and magnesium sulfate before aortic clamping, as well as additional factors. The only factor that had a significant association with paraplegia was cross-clamp time. The presence or absence of a shunt and the administration of vasodilators or other drugs had no significant effect on paraplegia development. However, because of the relatively small number of paraplegic patients, there is a possibility of failure of association of other factors.

A logistic model of probability relating the risk of paraplegia to cross-clamp time is shown in Figure 2. The calculated probability of paraplegia is less than 1% with a clamp time of 30 minutes and less than 5% with a clamp time of 45 minutes, but the curve rises steeply at 50 minutes. Although the average cross-clamp time in the Gott shunt patients was significantly longer than in the no-shunt patients, multivariate analysis indicated that a shunt did not offer protection from paraplegia or extend the "safe" cross-clamp time.

Comment

If survival of patients with blunt traumatic aortic disruption is to be improved, the diagnosis must be made promptly, methods to reduce the risk of rupture instituted, and urgent surgical repair carried out in most patients. If the aortic pseudoaneurysm ruptures, even if the patient is in the hospital, it is too late to salvage the patient. In this series, none of the patients who had aortic rupture with unobtainable blood pressure survived despite attempts at aortic clamping and resuscitation. Other authors have also noted the uniformly fatal outcome of patients with massive bleeding from aortic rupture [8, 9]. Perhaps a method of very rapid infusion of large volumes of blood could be of benefit in this situation [9]. However, with our current technology, the patient's best chance for survival is to arrive in the operating room with the pseudoaneurysm still intact.

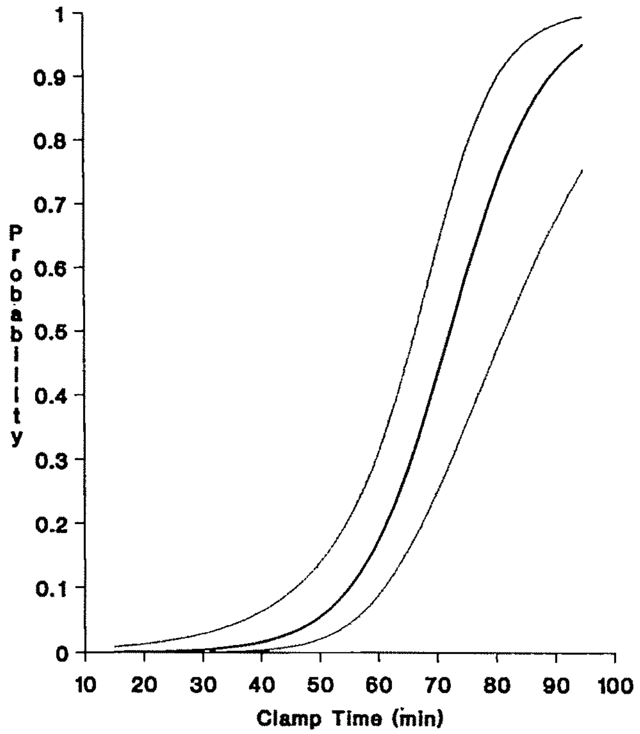

Fig 2. Logistic model of the probability of the occurrence of paraplegia compared with aortic cross-clamp time. The dotted lines *are 70% confidence limits.*

We have used early continuous arterial pressure monitoring and administration of drugs to decrease the forces applied to the aortic wall in patients suspected of having aortic disruption based on the history of the accident and mediastinal widening on chest radiographs. Thoracic computed tomographic scanning is omitted because it does not confirm or exclude aortic injury reliably. The patient is taken promptly to the angiography suite for an aortogram and is attended by surgical residents and special nurses who continue aggressive monitoring, volume administration, and blood pressure control. This early treatment method appears to be generally successful as only 1 patient in this series died of aortic rupture after aortography during transportation to the operating room, and he did not have a radial artery catheter and the vigorous treatment we now advocate.

Timing of aortic repair requires careful consideration and individualization. In most patients prompt aortic repair is indicated, as was done in 84% of the patients in this series. However, in 7 patients aortic repair was delayed 4 days to 4 months after aortography to allow stabilization of other injuries. The most frequent reason for delaying aortic operation was a severe head injury with either the need for intracranial operation or an uncertain prognosis on initial evaluation. Head injuries were responsible for the delay in 5 of the 7 patients. One patient had severe hypoxemia from pulmonary contusion and other injuries and could not have tolerated one-lung ventilation until his lung injury improved. One other delayed patient had electrocardiographic changes that were evaluated before repair. Although we did not encounter it in this series, another reason for delay could be presence of sepsis in a patient in whom the diagnosis of aortic injury is made late. The results from this series and our previously reported experience [7] support the safety of medical therapy in these highly selected patients, as none of them experienced aortic rupture while waiting for repair.

Prioritizing surgical procedures also requires careful consideration. Intracranial operation may have priority in the hemodynamically stable patient. In the patient in unstable condition with evidence of exsanguinating abdominal hemorrhage, laparotomy is indicated before aortic repair. If the airway is injured, this requires immediate attention. In this series, procedures prior to aortic repair were craniotomy or insertion of intracranial pressure monitors in 5 patients, laparotomy in 5 patients, and repair of tracheal laceration in 1 patient. The other 10 laparotomies and nearly all of the orthopedic procedures were performed after aortic repair. The only open fracture procedures done before aortic repair were in the delayed patients with head injuries.

Surgical repair of the aortic injury consisted of Dacron graft insertion in 95% of the cases because the aortic intima was completely or nearly completely transected and the ends separated. The intimal damage was substantially less than circumferential in only 2 cases, and these were both sutured directly. In most instances, sutureless intraluminal grafts were considered unsatisfactory because of the small diameter of the aorta in most of these young patients and lack of space distal to the left subclavian artery for seating of the proximal cuff.

The most controversial and unsolved aspects of descending aortic repair are the role of distal perfusion and the causes and incidence of paraplegia. During the period of this study, we used two techniques and the choice depended on the preference of the surgeon and the degree of stability of the patient. Forty-five percent of the patients had simple cross-clamping without distal perfusion, and in 55% a Gott shunt was placed with most patients receiving ascending to descending aortic shunting. No consistent effort was made to monitor distal aortic pressure or flow in shunted patients. Some patients received a variety of pharmacologic agents to possibly aid in spinal cord protection, and these included steroids, pentothal, magnesium sulfate, and mannitol. Nitroprusside was used for control of proximal hypertension if needed. Paraplegia occurred in 9.5% of the patients at risk, and there was no statistical difference between the incidence in the shunt and no-shunt groups (13% and 5.2%, respectively). Of all the variables evaluated by logistic regression analysis, the only factor significantly associated with paraplegia was cross-clamp time, and the association was a very strong one. Factors that had no association with paraplegia included admission systolic blood pressure less than 100 mm Hg, intraoperative hypotension, administration of nitroprusside or other vasodilators during aortic clamping, administration of drugs before aortic clamping that may protect the spinal cord, and presence or absence of a shunt. A most important variable that cannot be assessed preoperatively or by statistical analysis is the individual variation of spinal cord blood supply.

The length of the cross-clamp time is mainly a reflection of the complexity of the injury and the degree of difficulty of the repair; to a lesser extent it reflects the speed of the surgeon [10]. Problems leading to longer cross-clamp times in this series were difficulty with the proximal aorta with extension of the injury into the aortic arch close to the cross-clamp, and marked obesity of a patient with a very small aorta. Cross-clamp times in our patients in whom paraplegia developed were 70, 80, and 90 minutes in the shunted patients and 50 minutes in a no-shunt patient. Although the average cross-clamp time in the Gott shunt group was significantly longer than that of the no-shunt patients, logistic regression analysis indicated that the presence of a shunt had no additional protective effect for any given cross-clamp time. This finding is similar to that reported from the Maryland Shock Trauma Center [9] and different from that reported by the Alabama group [11].

We strongly endorse the efforts of investigators trying to improve the results of descending thoracic aortic operations, particularly with respect to reducing the incidence of paraplegia. It seems clear from our data and those of others that in the acute trauma situation, a Gott shunt without distal pressure or flow monitoring is not consistently protective of the spinal cord. We acknowledge that excellent results have been reported in predominately elective descending thoracic aortic aneurysm repairs using a Gott shunt with flow monitoring [12]. Partial cardiopulmonary bypass has its proponents, with evidence that spinal cord perfusion may be well maintained [13], but our past experience with systemic heparinization in acute trauma patients has been unsatisfactory because of hemorrhagic complications, making this an unacceptable method for use in this setting. Good results with left atrial–femoral bypass using a centrifugal pump without heparin have been reported in relatively small groups of patients [14, 15]. This approach appears promising in that flows similar to those of partial cardiopulmonary bypass can be obtained and heparin is avoided. Other adjuncts such as sensory evoked potential monitoring [16], spinal fluid drainage, and pharmacologic agents are probably of minimal help, especially in the acute trauma situation. The most desirable technique for these emergency operations in unstable patients with multiple injuries is a quick and uncomplicated method of aortic repair with a low mortality rate and as low a paraplegia rate as possible. In our hands, simple cross-clamping with graft insertion meets these criteria at the present time. We hope that with additional research, improvements can be made. However, because of variability in spinal cord blood supply and variability in extent and complexity of the aortic injury, the paraplegia rate will probably never be zero.

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DISCUSSION

DR FRANCIS ROBICSEK (Charlotte, NC): I thank The Society for the opportunity to discuss this thought-provoking report. As far as the methodology is concerned, I have a few questions, all related to the lack of randomization.

This study encompasses a period of 14 years. Is there a bias in comparing earlier Gott-shunted cases with more recent nonshunted cases? Also, the shunted group had a much higher paraplegia rate but also a much longer cross-clamp time. Is it possible that the more severely injured patients were shunted and the less severely injured patients were not shunted? I would also like to call attention to the fact that we are more or less fighting a strawman opponent, because a question in the mind of most of us is not to shunt with a Gott shunt or just simply cross-clamp and sew, but to use other bypass methods such as Bio-Medicus or Bio-Medicus–type bypass systems.

In the material we have collected with my partner, Phillip Hess, we have 36 patients who survived reconstructive operation for traumatic aortic rupture. Femoral vein to femoral artery oxygenated bypass was used in 5. None of these patients suffered paraplegia, but we had two late deaths. Sixteen patients were operated on using a simple cross-clamp without shunt. Of the 16, 4 had paraplegia, 4 had renal shutdown, and 5 died late. Recently we have operated on a series of 15 patients using nonanticoagulated left atrium to femoral artery bypass, with cross-clamp times ranging from 21 minutes to 2 hours. There was neither death nor paraplegia in this system. We were also disturbed that in the simple clamp, no-shunt groups, we had 2 patients with less than 32-minute cross-clamp times who ended up with paraplegia.

We certainly are not here to dispute the virtues of fast and expeditious operation. Reconstruction of the ruptured aorta in a very short time is possible in some cases by some surgeons but not in all situations for all surgeons. And even if it is possible to do it in such a short time, in our experience, contrary to Hilgenberg and associates, we believe that whenever the clinical situation allows, nonanticoagulated left atrium to femoral artery bypass may provide some additional protection against the most feared complication of paraplegia.

I learned a lot about this complication by serving on your Committee on Medico-Legal Affairs, and I found that about one third of major malpractice suits involving cardiovascular thoracic operations were connected to nonshunted paraplegias stemming from descending aortic reconstruction. I think the Bio-Medicus shunt is a very valuable protection not only for the patient's lower spine but also for that of the surgeons.

DR STEPHEN Z. TURNEY (Baltimore, MD): I compliment Dr Hilgenberg and associates on their comprehensive report and congratulate them on their results. We recently reported our own updated experience of 114 patients from Baltimore at the meeting of the Association for Thoracic Surgery and came to essentially the same conclusions, that morbidity and mortality are high and are complex problems. Aortoaortic shunt does not necessarily protect patients from paraplegia. It is our practice not to routinely use shunt.

A natural history survival curve for blunt thoracic aortic rupture shows that most deaths occur within 12 to 24 hours of injury. Very early transport of the accident victim, as in our trauma systems, pushes the patient population one is faced with to the steep, high mortality rate portion of the curve where patients are exsanguinating from their aortic and other injuries. The other risk factors we identified included hypotension on admission, a large presenting hemothorax, the surgeon's credentials, and the presence of other serious injury.

My question is, does early pharmacologic intervention present problems of its own in management, such as the evaluation of hidden bleeding, large blood pressure swings as anesthesiologists struggle to regulate blood volume and pressure, or the steal of blood from the spinal cord during cross-clamping? We scrupulously snare intercostal arteries to avoid back-bleeding and cord steal during repair, but we remain concerned that pharmacologic steal may be taking place into a dilated, low-pressure, systemic vascular bed if the patient is receiving vasodilators.

DR MANUEL DE JESUS ANTUNES (Coimbra, Portugal): In their well-presented large series, Dr Hilgenberg and associates have clearly demonstrated that the length of the aortic cross-clamping is the most important risk factor for paraplegia, irrespective of the technique used. That much had also surfaced from a review of the literature done from our previous institution by Dr Svenson some years ago. Hence, all technical details that may help reducing the cross-clamp time will be of major importance.

In an article published in *The Annals* 3 years ago, I suggested that using straight aortic cross-clamping without shunts or cardiopulmonary bypass and incision of the descending aorta, including the covering hematoma in the area of rupture, would expose the tear, usually located on the opposite wall when the tear was partial. The tear could then be repaired, from within the lumen of the aorta, more clearly and easily with a continuous suture without further dissection. When there was complete separation of the aortic edges, the repair could also be facilitated by working from inside the lumen, either with direct approximation or by interposition of a graft. Finally, the latter could also be made easier by incising it longitudinally and transforming it into a circular patch. Using these techniques, we have now operated on 17 consecutive patients without paraplegia and with only 1 case of transient paraparesis. I believe that this is a consequence of a short mean aortic cross-clamp time of 22 minutes with a range not exceeding 27 minutes.

I congratulate Dr Hilgenberg and associates on their fine work. Dr Hilgenberg, what is your current preference of technique with regard to the protection of the spinal cord?

DR HILGENBERG: Controversies and unsolved issues continue to involve the management of thoracic aortic injuries, and I am pleased to see this amount of discussion. I will attempt to answer some of the questions.

Dr Robicsek, there was a general trend over this 14-year period toward the use of shunts more frequently in the earlier years and less so in the later years. Your analysis of that point is correct. However, there were some shunted patients even in the most recent years. The shunts were placed based on the preference of the surgeon and the stability of the patient's condition. I cannot explain why the cross-clamp times were longer in the shunted patients. Because it is unusual for the surgeon to determine exactly how complex the proximal aortic injury will be until after the clamps are on and the aorta is open, I do not believe that there was a bias toward insertion of shunts in the more complex patients.

We are impressed with some of the data from Stanley Crawford's recently published experience. The cases were elective descending aneurysms and not aortic trauma cases, but he looked carefully at distal perfusion with the Bio-Medicus pump and somatosensory evoked potential monitoring, and he found that those methods did not appear to confer increased protection against paraplegia. The fact remains that there are variables that we cannot necessarily predict with respect to the spinal cord and its function and blood supply.

Dr Turney, we are aware of your large experience with aortic injuries, and I was pleased to see that our data and results correspond very closely with yours. Regarding early pharmacologic intervention, we have attempted to do this judiciously, and we have not experienced major swings in blood pressure. We were also concerned about spinal cord perfusion and nitroprusside administration during cross-clamping, and we looked at this carefully with multivariate analysis. It was not a significant factor associated with paraplegia.

Dr Antunes, we rarely see injuries that are less than circumferential. Perhaps there is some difference in our patient populations. There were only 2 patients out of 44 in this series in whom we thought the aortic injury was so localized that it could be easily repaired by direct suture. We usually insert a graft because the injuries are so frequently circumferential with separation of the aortic ends.

University of Wisconsin Solution for Pulmonary Preservation in a Rat Transplant Model

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University of Wisconsin and modified Euro-Collins solutions for pulmonary preservation were compared in a rat orthotopic left lung isotransplant model. Heart-lung blocks of donor rats were flushed with and preserved in one of the preservation solutions at 0°C. After 6 or 12 hours of cold ischemia, the left lungs were transplanted into recipient rats and reperfused for 1 hour. Pulmonary function was assessed by measuring oxygen and carbon dioxide tensions in arterial blood after removal of the right lung. Lipid peroxide concentrations were measured as thiobarbiturate acid–reactive substances. The ratios of wet to dry weight of grafts after ischemia and after reperfusion were calculated. Histologic changes of ischemia-reperfusion injury of the lung tissue were evaluated using a graded scale. Oxygen tension after 6 hours of preservation followed by reperfusion was significantly higher with University of Wisconsin solution (308.8 ± 81.1 mm Hg) than with Euro-Collins solution (50.8 ± 17.8 mm Hg; $p < 0.001$). Carbon dioxide tension in the University of Wisconsin solution group was also significantly lower than in the Euro-Collins solution group (28.2 ± 2.3 versus 46.0 ± 4.5 mm Hg; $p < 0.05$). Lipid peroxide concentration after 6 hours' preservation in University of Wisconsin solution was significantly lower (0.88 ± 0.07 μmol/g) than that in Euro-Collins solution (1.26 ± 0.12 μmol/g; $p < 0.05$). After 12 hours of preservation only lipid peroxide concentration with University of Wisconsin solution was significantly lower (1.30 ± 0.09 μmol/g) than with Euro-Collins solution (1.71 ± 0.15 μmol/g; $p < 0.05$). There were no differences in the other variables. We conclude that University of Wisconsin solution provides superior lung preservation than does Euro-Collins solution in this transplant model.

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Since 1981, when the first successful heart-lung transplantation was performed [1], lung transplantation has become an accepted treatment option for a variety of pulmonary diseases [2]. The major factor limiting the expansion of lung transplantation is the restricted availability of donor organs. With the prospect of increasingly longer travel for a limited supply of donors, good preservation of the graft during the period of ischemia becomes of paramount importance. Our ability to adequately preserve pulmonary grafts in clinical lung transplantation lags far behind that of other solid organs such as liver and kidney, where greater than 12 hours of ischemia is well tolerated, and even hearts, which have acceptable ischemic times of 6 to 8 hours. Although some techniques of pulmonary preservation including autoperfusion of the heart and lungs using a modified Starling apparatus [3] and core-cooling of the entire donor with hypothermic cardiopulmonary bypass [4, 5] have been reported, they have not gained widespread acceptance. Static ex vivo preservation using pulmonary artery flush is currently the most popular method of preservation. Much work on chemical modification of preservation solutions has been done in an attempt to obtain more reliable preservation, to reduce the severity of reperfusion injury, and to extend the period of ischemia [6–8]. Modified Euro-Collins solution (EC) was established by the Stanford group for on-site donor procurement at first [9]. Since adequate preservation of canine lungs up to 6 hours was reported using EC [10], EC has been the most widely used flush solution for lungs. Although subsequent clinical reports confirmed its efficacy for distant donor procurement [11, 12], EC also yields unpredictable results [13].

Recently, University of Wisconsin solution (UW) has been reported to offer extended cold preservation ability in other organs [14–16]. The aim of the present study was to evaluate UW solution for pulmonary preservation.

Material and Methods

Animals

Specific pathogen-free inbred male Lewis rats weighing 300 to 350 g (Charles River Breeding Laboratories, Wilmington, MA) were used as both donor and recipient animals. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" published by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health publication No. 85-23, revised 1985).

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Table 1. Compositions of Solutions Used to Flush Pulmonary Artery and Store Lungs

Component	EC	UW
Potassium	107 mmol/L	125 mmol/L
Sodium	9.3 mmol/L	30 mmol/L
Magnesium	4.7 mmol/L	5 mmol/L
Chloride	14 mmol/L	. . .
Bicarbonate	9.3 mmol/L	. . .
Phosphate	55 mmol/L	25 mmol/L
Sulfate	4.7 mmol/L	5 mmol/L
Lactobionate	. . .	100 mmol/L
Raffinose	. . .	30 mmol/L
Glutathione	. . .	3 mmol/L
Adenosine	. . .	5 mmol/L
Allopurinol	. . .	1 mmol/L
Glucose	5.6%	. . .
Mannitol	0.58%	. . .
Hydroxyethyl starch	. . .	5.0%
Insulin	. . .	100 U/L
Dexamethasone	. . .	8 mg/L
pH	7.74	7.87
Osmolality	452 mOsm/L	327 mOsm/L

EC = modified Euro-Collins; UW = University of Wisconsin.

Experimental Protocols

In the control group (n = 7), lungs were flushed with isotonic saline solution and donor lungs were transplanted immediately. In the EC-6 (n = 6) and EC-12 (n = 6) groups, the pulmonary artery was flushed with EC (Table 1) and the lungs were stored in EC for 6 and 12 hours, respectively. In the UW-6 (n = 7) and UW-12 (n = 6) groups, the pulmonary artery was flushed with UW (see Table 1) and the lungs were stored in UW for 6 and 12 hours, respectively.

Operative Techniques

To perform orthotopic left lung transplantation in the rat, we have modified surgical techniques described by other investigators [17–19].

Donor rats were lightly anesthetized by inhalation of methoxyflurane and then intubated orally with a 6.4-cm (2½-inch) 14-gauge angiocatheter. The catheter was premeasured so that the tip of the catheter was just proximal to the carina when the Luer fitting was at the level of the incisors, thus permitting safe bilateral ventilation. Animals were then connected to a rodent ventilator (model 683; Harvard Apparatus, South Natick, MA), which was adjusted to maintain normal ventilation (respiratory rate, 70/min; tidal volume, 10 mL/kg body weight; positive end-expiratory pressure, 5 cm H_2O; peak inspiratory pressure, 20 cm H_2O). Anesthesia for the surgical procedure was maintained with a 2% halothane mixture delivered by 100% oxygen at a flow rate of 0.5 L/min. An operating microscope with 6 to 16 times magnification (M-650; Wild Heerburgg Ltd, Heerburgg, Switzerland) was used for the procedure. The operation was performed using clean, nonsterile technique by a single surgeon (R.A.).

Donor animals received heparin (300 U) injected intravenously. Through a median sternotomy, the thorax was exposed and the inferior pulmonary ligaments were carefully divided. A 16-gauge catheter was inserted into the main pulmonary artery through the right ventricle. Immediately after the inferior vena cava was divided and the left and right atrial appendages were amputated, the pulmonary artery was flushed with 100 mL/kg of one of the cold (0°C) preservation solutions from a height of 30 cm, and the thorax was irrigated with cold (0°C) normal saline solution. The donor heart and lungs were then removed en bloc. Before division of the donor bronchus, a hemostatic clip (Hemoclip; Edward Weck and Co, Research Triangle Park, NC) was placed across the trachea to maintain lung inflation. The heart-lung block was wrapped in a bed of gauze soaked with 0°C preservation solution, placed in a plastic container surrounded by ice, and stored in a refrigerator. The organs were thus maintained at 0°C for the duration of the ischemic storage period. Before implantation the left pulmonary artery, pulmonary vein, and main bronchus were dissected, and the left lung was taken by dividing the hilar vessels as proximally as possible to obtain sufficient length for the cuffs and dividing the left main bronchus appropriately for the anastomosis later. A cuff was attached to the pulmonary vein first. The cuffs were made from segments of 16-gauge polyethylene tubing and consisted of a body 1 mm in length and a 1-mm extension. The donor pulmonary vein was passed through the cuff with the extension directed to the backside of the vessel. The proximal end of the vein was everted over the cuff and then firmly fixed with a circumferential ligature of 7-0 cardiovascular silk. The pulmonary artery was cuffed in the same way.

The recipient animal was then anesthetized, intubated, and ventilated with the same procedure and ventilator conditions as the donor. The recipient was placed in the left-side-up position and a left thoracotomy was performed at the fifth intercostal space. The inferior pulmonary ligament was carefully divided. After the hilar structures were dissected, the lung was clamped with a curved vascular clamp and gently retracted to expose the hilum. After the recipient hilum was cross-clamped proximally, a small venotomy was made in the posterior wall of the distal pulmonary vein. The pulmonary vein was flushed with heparinized saline solution to prevent thrombosis. The cuff of the graft pulmonary vein was inserted into the incised pulmonary vein of the recipient and fixed with a circumferential ligature of 7-0 cardiovascular silk to complete the anastomosis. The pulmonary artery was connected to the graft in the same way, after which the cross-clamp was removed and reperfusion was established. The bronchial anastomosis was completed with 8-0 polypropylene using continuous and interrupted sutures for the cartilaginous and the membranous portion, respectively.

The lungs were hyperinflated to remove atelectasis from the donor lung, after which the proximal airways were suctioned to clear secretions. Animals were ventilated with 100% oxygen for the duration of the 1-hour reperfusion period.

Evaluation of Pulmonary Preservation

After the reperfusion period, the recipient's thorax was exposed through a median sternotomy. Tidal volume was reduced to 5 mL/kg, and the right lung was removed, thus making the animal dependent on the transplanted lung. After a 5-minute period of equilibration, arterial blood was withdrawn through the left ventricle and oxygen and carbon dioxide tensions were measured with a blood gas analyzer (ABL-2; Radiometer, Copenhagen, Denmark). The animal was then exsanguinated and samples of the reperfused (transplanted) lung were harvested.

Samples of the right lung of the donor animal were taken to evaluate the effect of flush and cold ischemia only. The transplanted left lung was excised at the termination of the reperfusion period to determine reperfusion injury. Samples of both ischemia only and ischemia-reperfusion lungs were used for assay for lipid peroxide, gravimetric measurement, and histologic examination.

Approximately one third of the lung was frozen in liquid nitrogen and kept at -70°C for the measurement of lipid peroxide. Thiobarbituric acid–reactive substances were measured according to the method of Ohkawa and associates [20] using 10% weight/volume homogenates. Standard curves were obtained from measurement of different concentrations of 1,1,3,3-tetramethoxypropane and the results were expressed as micromoles of 1,1,3,3-tetramethoxypropane per gram of dry tissue per hour.

Approximately one half of each lung was used for determination of wet weight to dry weight ratio using an electronic balance (model AE240; Mettler, Highstown, NJ). Weights were measured immediately after the lung was excised and then after drying in a heating oven for 24 hours at 80°C.

A portion of each lung was stored in formalin for light microscopic analysis and stained with hematoxylin and eosin. A pulmonary pathologist (S.A.Y), who was blinded to the experimental group, scored the histologic level of preservation and reperfusion injury according to the following scaling system: grade 0, no abnormal findings; grade 1, patchy alveolar edema with widened interstitium with occasional erythrocytes in air spaces; grade 2, patchy hemorrhage and diffuse alveolar edema with widened interstitium, rare infrequent hyaline membranes, vacuolation, and hobnail change of endothelium; grade 3, widespread hyaline membranes coating alveolar septa with hemorrhage and endothelial vacuolation accompanied by sloughing and fibrin microthrombi; grade 4, diffuse alveolar hemorrhage, hyaline membranes, massive hemorrhage and necrosis of parenchyma, and vascular necrosis.

Statistical Analysis

Results were expressed as the mean ± standard error of the mean. All data of continuous variables were subjected to analysis of variance with Scheffé probability testing. If the overall analysis of variance was statistically significant at the 0.05 level, the post-hoc analysis was performed to determine the significance of differences between mean values of two groups. The Kruskal-Wallis χ^2 test followed by the Mann-Whitney U test were used for the analysis of histology because of the noncontinuous nature of the data. Differences were considered significant if the p value was less than 0.05.

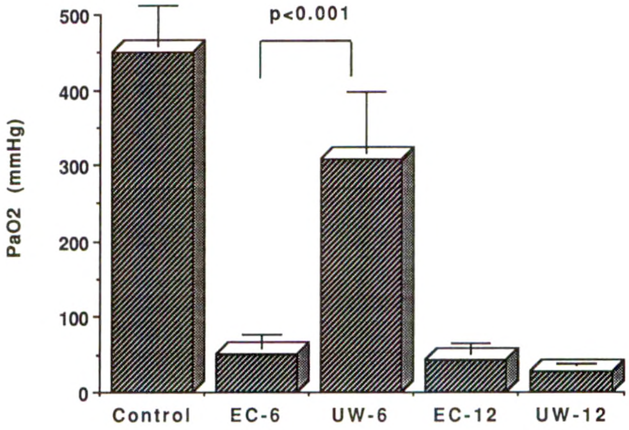

Fig 1. Oxygen tension (PaO2) in arterial blood (100% O_2) after ischemia followed by reperfusion. Data are shown as mean ± standard error of the mean. (See text for description of groups.)

Results

The mean ischemic time from the beginning of the pulmonary artery flush to the initiation of reperfusion was 54 ± 2 minutes in the control group. There were no significant differences between those in the EC-6 and UW-6 groups (359 ± 6 versus 364 ± 2 minutes) or between the EC-12 and UW-12 groups (759 ± 12 versus 764 ± 10 minutes).

In the control group, oxygen tension after 1 hour of reperfusion was 451 ± 54 mm Hg; this was significantly ($p < 0.05$) greater than that of all other experimental groups but the UW-6 group (Fig 1). After 6 hours of preservation, oxygen tension in the UW-6 group averaged 309 ± 81 mm Hg, which was significantly ($p < 0.001$) higher than that achieved by the EC-6 group (51 ± 18 mm Hg). By 12 hours of preservation, however, neither solution yielded acceptable results, with oxygen tensions of 43 ± 15 mm Hg in the EC-12 group and 27 ± 3 mm Hg in the UW-12 group.

The results for carbon dioxide tension (Fig 2) paralleled those for oxygen tension. Carbon dioxide tension in the control group remained at 29.1 ± 4.7 mm Hg, and all other groups except the UW-6 group showed significantly ($p < 0.05$) more hypercapnia than the control group. After 6 hours of ischemia, carbon dioxide tension in the UW-6 group was 28.2 ± 2.3 mm Hg, which was significantly ($p < 0.05$) lower than that in EC-6 group (46.0 ± 4.7 mm Hg). Carbon dioxide tension was also similar in the EC-12 and UW-12 groups (52.4 ± 8.5 versus 47.7 ± 7.0 mm Hg, respectively).

Assay of lipid peroxide content showed no significant

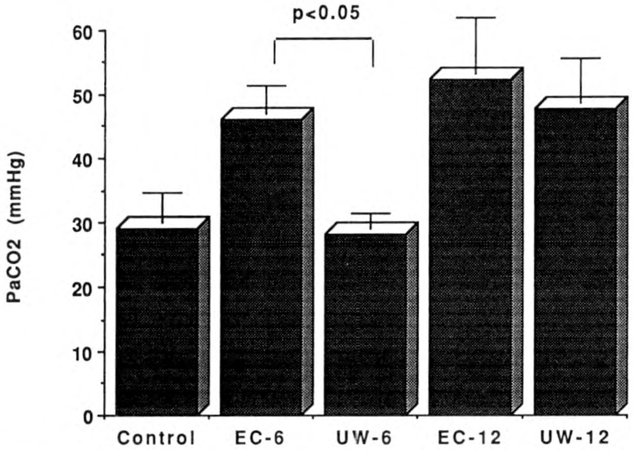

Fig 2. Carbon dioxide tension in arterial blood (PaCO2) *after ischemia followed by reperfusion. Data are shown as mean ± standard error of the mean. (See text for description of groups.)*

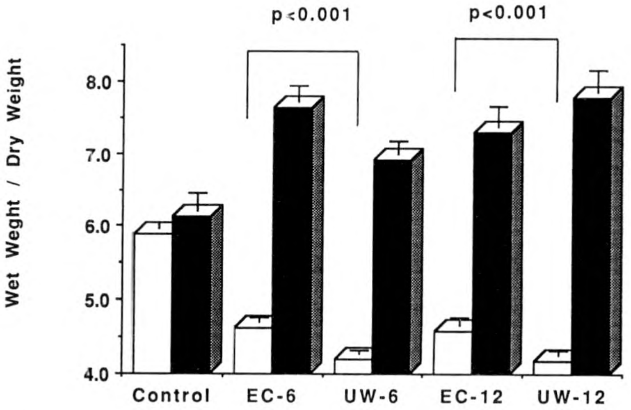

Fig 4. Wet weight to dry weight ratio of the lung tissue after ischemia (white bar) *and ischemia followed by reperfusion* (black bar). *Data are shown as mean ± standard error of the mean. (See text for description of groups.)*

intergroup differences by analysis of variance after ischemic storage only ($p = 0.55$). Ischemia followed by reperfusion caused significant ($p < 0.05$) increase in lipid peroxide levels in the control and all experimental groups (Fig 3). Lipid peroxide level in the control group was 0.93 ± 0.18 μmol/g, which was significantly ($p < 0.05$) lower than those in the EC-12 ($p < 0.001$) and UW-12 ($p < 0.05$) groups. The UW-6 value remained at 0.88 ± 0.07 μmol/g, and this was significantly ($p < 0.05$) lower than that in the EC-6 group (1.26 ± 0.12 μmol/g). Lipid peroxide content in the UW-12 group rose to 1.30 ± 0.09 μmol/g, which was still significantly ($p < 0.05$) lower than that in the EC-12 group (1.71 ± 0.15 μmol/g). On the other hand, comparing the same preservation solution groups at different preservation times, the levels of lipid peroxide in the EC-12 and UW-12 groups were significantly higher than those in the EC-6 and the UW-6 groups ($p < 0.05$ for each comparison).

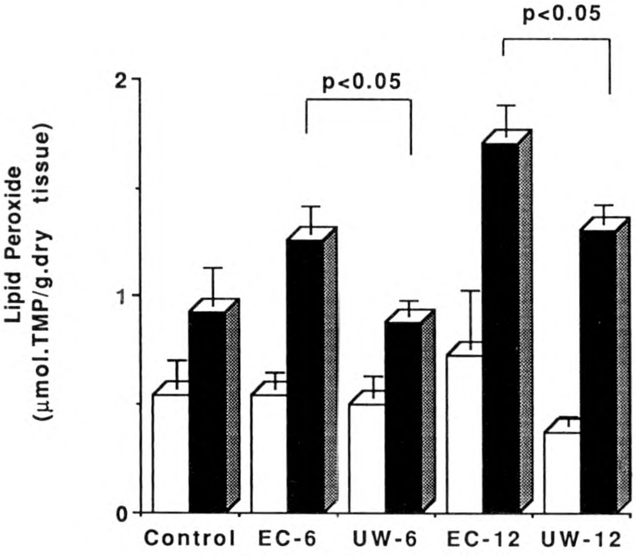

Fig 3. Lipid peroxide concentration in lung tissue as thiobarbituric acid–reactive substances after ischemia (white bar) *and ischemia followed by reperfusion* (black bar). *Data are shown as mean ± standard error of the mean.* (TMP = *1,1,3,3-tetramethoxypropane; see text for description of groups.)*

After ischemic storage only, the wet/dry weight ratio in the control group averaged 5.88 ± 0.09, which was significantly ($p < 0.001$) higher than that of all other groups (Fig 4). The wet/dry weight ratio in the UW-6 (4.21 ± 0.03) and UW-12 (4.18 ± 0.06) groups were significantly ($p < 0.001$ for each comparison) lower than those of the EC-6 (4.63 ± 0.06) and EC-12 (4.58 ± 0.10) groups. After ischemia followed by reperfusion, the wet/dry weight ratio in the control group remained at 6.12 ± 0.26, which was significantly ($p < 0.05$) lower than those in all other groups. The wet/dry weight ratio in the EC-6 group increased to 7.63 ± 0.22, which tended to be higher than that in UW-6 group (6.92 ± 0.18), although this difference did not reach significance. The EC-12 and UW-12 groups had similar values of wet/dry weight ratio (7.29 ± 0.28 and 7.77 ± 0.31, respectively).

After ischemic storage, the Kruskal-Wallis test showed no intergroup differences in histologic injury scores. After ischemia and reperfusion, the score of lung injury in the control group was significantly ($p < 0.05$) lower than in all other groups (Fig 5). No differences were detected in histologic injury scores between the EC-6 and UW-6 groups or between the EC-12 and UW-12 groups.

Comment

This study compared the ability of EC, currently the most widely used clinical pulmonary flush solution [11, 12], and UW, which gives excellent preservation in other solid organs [14–16], to adequately preserve lungs in a rodent pulmonary transplant model. University of Wisconsin solution and EC have several features in common. Both are essentially intracellular solutions of electrolytes having high potassium and low sodium concentrations. They each contain KH_2PO_4 hydrogen ion buffer to suppress intracellular acidosis caused by anaerobic glycolysis during ischemia. Magnesium ion is added as a membrane stabilizer

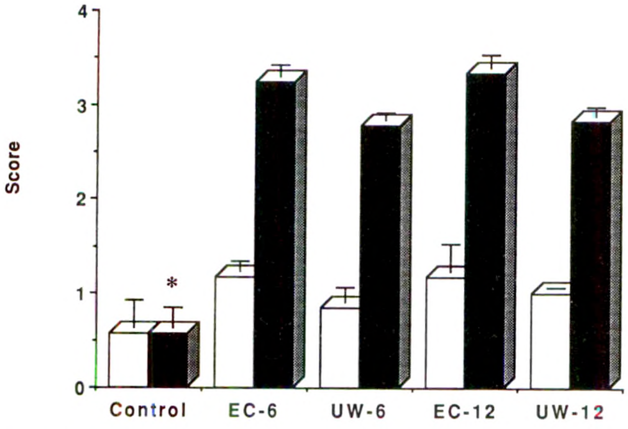

*Fig 5. Histologic score for lung injury (0 to 4) after ischemia (*white bar*) and ischemia followed by reperfusion (*black bar*). Data are shown as mean ± standard error of the mean. (*Asterisk *indicates significant differences after reperfusion between the control group and all other experimental groups [*p *< 0.05].) (See text for description of groups.)*

University of Wisconsin solution, however, contains several theoretically beneficial constituents that are not in EC. From a physiological point of view, lactobionate and raffinose, both nonpermeable and nonmetabolizable large molecular weight anions, are potent osmotic agents. The benefit of these agents in suppressing cell swelling has been shown in pancreatic tissue [21]. Hydroxyethyl starch is added to produce colloid osmotic pressure and prevent interstitial edema. Swelling of endothelial and alveolar cells, and expansion of the interstitial space, are reflected by an increase in the wet/dry weight ratio. Our data demonstrated a reduced wet/dry weight ratio in the UW-6 group, indicating that UW was superior to EC in suppressing pulmonary cellular and interstitial edema. The expansion of alveolar cells and interstitial space also impairs gas exchange at the alveoli-capillary level. The beneficial effect of UW in preserving gas exchange, at least to 6 hours, is shown in this study.

Allopurinol, a xanthine oxidase inhibitor, is added to suppress free radical generation. Glutathione is also effective in reducing a variety of cytotoxic oxidants. Oxygen free radicals are generated in conversion of hypoxanthine to xanthine in the reperfusion period after ischemia. These radicals are converted to hydroxyl radicals ($OH^{\cdot}$), which are highly reactive with a variety of biosubstances. Lipid peroxides made in this way are thought to greatly contribute to tissue damage. In our study, increases in tissue lipid peroxide were seen in parallel with deterioration of gas exchange and increases of lung water content. This study also demonstrated that UW suppressed the production of lipid peroxide after reperfusion to a greater degree than EC.

Euro-Collins solution is reported to cause elevation of pulmonary vascular resistance and decreased pulmonary compliance with cold pulmonary artery flush [22], which might cause uneven preservation of the lung graft and aggravate ischemia-reperfusion injury, although the mechanism of this phenomenon has not been clarified. It is not known whether UW also causes vasoconstriction; however, its higher viscosity could be beneficial by providing more even distribution of preservation solution into constricted resistance vessels.

This is one of few reports in which a rat model was used for evaluation of pulmonary preservation. In most previous studies evaluating the effectiveness of pulmonary preservation solutions during cold ischemia, larger animals such as dogs and pigs have been used as single-lung [6–8] or double-lung [23] transplant models. The major feature of these models is that adequacy of gas exchange in the pulmonary graft can be assessed by making the recipient totally dependent on the transplanted lungs. Although our model in the rat offers the same advantage as these other studies, it is much less expensive, can be completed more rapidly, and, most importantly, can eliminate the confounding variable of rejection by use of isogeneic transplants. Isolated in vitro lung models have been used for this purpose also [22, 24]. In these models, however, leukocytes might be impaired, if not absent. Leukocytes have been reported to play a key role in reperfusion injury of the postischemic lung [25], in which they are activated by free radicals and are sequestrated in the lung, where they produce more free radicals. An additional disadvantage of in vitro techniques is that oxygen and carbon dioxide tensions in the reperfusion fluid are not necessarily physiologic. These models therefore introduce bias into their experimental results. We believe that our single-lung isogeneic transplantation model in the rat provides the optimal parallel to clinical lung transplantation and is suitable for assessing pulmonary preservation solutions with cold ischemia.

One of the most important considerations in the present study is that the time of acceptable preservation was relatively short. It is inappropriate to directly compare our data with other experimental reports demonstrating successful preservation for more than 12 hours in canine models [6, 7, 23]. No reports are available concerning the difference in metabolic rates of lung tissue among species. However, judging from a recent report in which it was demonstrated that the rate of catabolism of adenine nucleotide of rat myocardium was two or more times that in dogs [26], the sensitivity to ischemic insult in rat lungs could also be much greater than that in dogs. On the other hand, Pickford and colleagues [27], using almost the same model as ours, showed that pulmonary grafts after 48 hours of preservation produced highly consolidated chest roentgenograms in the first postoperative week and then improved and functioned 5 weeks after transplantation. Those lung grafts might fail in function in the early phase of reperfusion because they were subjected to ischemia-reperfusion injury or surgical trauma, and then recover functionally. We have demonstrated that transplanted rat lung grafts preserved appropriately do function excellently in the early period of reperfusion, as has been shown in reports using larger animals.

In conclusion, the present study clearly demonstrated that UW preserved pulmonary graft function more effectively than EC at least to 6 hours, and that preservation with UW was accompanied by decreased production of lipid peroxide. The rat isogeneic single-lung transplant procedure offers a rapid and reliable model to evaluate the pulmonary graft after cold ischemia followed by reperfusion.

Dr Aeba is a recipient of the American Heart Association Research Fellowship Award.

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DISCUSSION

DR THOMAS M. EGAN (Chapel Hill, NC): Your 6-hour Euro-Collins animals contradict results from other centers using large animal models that can produce good lung function after 6 hours preservation with Euro-Collins solution, and frankly, they contradict the clinical experience that most of us have, that 6 hours is well tolerated if a Euro-Collins flush is employed. First of all, can you address that contradiction? Second, did you use prostaglandin E_1 or inflate the lungs for storage?

DR AEBA: To answer the first question, I have to mention the species differences. As you may know, the rat has been reported to have a higher activity of xanthane oxidase, which is a key enzyme of lipid peroxidation, and higher metabolic degradation of adenosine triphosphate than do dogs, pigs, and humans in a variety of organs, including the lung. That is why the rat is much more sensitive to ischemia-reperfusion injury than larger animals. So I do not think it is appropriate to directly compare our data with other experimental reports demonstrating successful preservation for more than 12 hours in a canine model. Our final goal is to get better preservation methods.

As to the second question, I did not use prostaglandin E_1; however, I kept my graft lungs in an inflated state during the entire period of preservation.

DR WILLIAM A. BAUMGARTNER (Baltimore, MD): You certainly are to be congratulated on carrying out a very difficult experiment. These are tough, technical exercises. I had the same worry that Dr Egan had in that the majority of clinical experience would suggest that 6 hours and maybe even above that provides good protection for clinical lung transplantation. Perhaps your results were related to some technical aspect such as a lack of pulmonary vasodilatation at the time in which the cold solution was instilled, because I think there is a known vasoconstrictor response to hypothermia.

One thing I think your study does show is that there still is a need for better preservation for beyond 6 hours. Clearly in your model UW did not effectively preserve lungs at that time.

I have two questions. The first is that there have been data suggesting that if you switch the ratio of sodium and potassium in the UW solution, pulmonary preservation may be in fact enhanced. Do you have any comment on that? And the second is, has the Pittsburgh group now gone to using UW solution clinically, and if so, can you give us some follow-up on that?

DR AEBA: Thank you, Dr Baumgartner. First of all, I tried low-potassium UW solution several times; however, I failed to find a difference between results with higher and lower potassium levels. As to the second question, so far in our clinical data for UW we have a good feeling that, especially just after 1 or 2 postoperative days, the chest roentgenogram is pretty good, at least better than in the era of Euro-Collins solution.

Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

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Activated Neutrophils Impair Rabbit Heart Recovery After Hypothermic Global Ischemia

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Cardiopulmonary bypass is known to cause neutrophil activation, and activated neutrophils appear to be of importance in myocardial reperfusion injury. This study examined the effect of a preischemic infusion of activated neutrophils on the recovery of myocardial function after 40 minutes of hypothermic global ischemia. Studies were carried out in three groups of Langendorff-perfused rabbit hearts: control, control (unactivated) neutrophil infusion, and phorbal myristate acetate–activated neutrophil infusion. The activated neutrophil group showed significant deterioration in function during the activated neutrophil infusion. All three groups demonstrated significant depression of function initially after reperfusion, but the two control groups subsequently recovered to baseline levels. The activated neutrophil group, however, showed a persistent significant depression in ventricular force, rate of ventricular tension development, and rate of ventricular relaxation as well as a significant increase in coronary vascular resistance. It is concluded that activated neutrophils depress myocardial function and contribute to impaired recovery of function after global hypothermic ischemia.

(Ann Thorac Surg 1992;53:247–52)

There are a number of mechanisms whereby neutrophils undergo activation during cardiac operations. The use of cardiopulmonary bypass has been clearly shown to result in systemic complement activation. Chenoweth and associates [1] demonstrated that C3a levels were significantly increased within 10 minutes of initiation of bypass and that levels continued to rise steadily thereafter until bypass was terminated. Subsequent studies by other investigators have confirmed this finding [2–7]. The complement activation factor C5a binds to neutrophil receptors and initiates a number of activation responses, which include chemotaxis, aggregation with increased endothelial adherence, release of lysosomal enzymes, and superoxide anion production [3]. Cardiopulmonary bypass has also been shown to increase the level of plasma kallikrein, which is known to induce neutrophil chemotaxis, aggregation, and degranulation [8]. The ischemic/reperfused myocardium may itself be an additional source of complement activation [9], as well as a target for activated neutrophils.

A great deal of interest has recently been focused on the role of leukocytes as mediators of myocardial reperfusion injury. Neutrophil depletion induced by a variety of mechanisms including pharmacologic agents [10], antineutrophil antibodies [11], leukocyte filters [12], or a combination thereof [13] has been shown to decrease infarct size in animal models. Experimental infarct size has also been decreased by the use of specific monoclonal antibodies to prevent neutrophil endothelial adherence [14] and by agents known to inhibit neutrophil migration and function [10]. Neutrophil depletion of the reperfusate resulted in a highly significant improvement in contractile function in the piglet heart subjected to extended hypothermic preservation [15].

Previous work from this laboratory has demonstrated a significant deterioration in function in isolated rabbit hearts perfused with activated neutrophils [16]. The present study was undertaken to extend these observations using a protocol of hypothermic ischemic arrest followed by normothermic reperfusion more analogous to the conditions employed during cardiac operations.

Material and Methods

Studies were carried out in male New Zealand rabbits 1.5 to 2.0 kg in weight. Rabbits were housed in the animal care facility of Victoria Hospital and were given free access to food and water. Treatment of animals used in this study conforms to the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985) and to the guidelines of the Canadian Council on Animal Care.

Neutrophil Preparation

Eighteen-milliliter aliquots of whole blood were obtained from rabbit donors by direct cardiac puncture using a 20-mL syringe containing 2 mL of 3.8% sodium citrate. The citrated blood was centrifuged at 240 *g* for 5 minutes and the platelet-rich plasma layer discarded. The remaining cells were resuspended in 6% dextran in 0.9% saline solution to sediment erythrocytes, and the plasma layer was centrifuged at 400 *g* for 10 minutes. The resulting

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pellet was resuspended in Hank's buffer containing 0.5% human serum albumin and overlaid on a Ficoll gradient. After centrifugation at 600 *g* for 20 minutes, the pellet was again suspended in Hank's buffer and any remaining erythrocytes lysed by addition of distilled water. The cells were then resuspended in Hank's buffer and counted using a gentian violet stain. The remaining cell population was greater than 95% neutrophils, and cell viability as assessed by trypan blue exclusion was consistently greater than 95%.

Phorbol myristate acetate (PMA) in dimethyl sulfoxide (1 mg/mL) was used for neutrophil activation. Previous pilot studies using simultaneous infusions of PMA and neutrophils resulted in significant deterioration in myocardial function, but data from control studies using infusions of PMA alone suggested that the PMA itself was contributing to this myocardial dysfunction. Accordingly, the protocol was altered so as to activate the neutrophils and then remove PMA from the suspending solution. Freshly isolated neutrophils were suspended for 5 minutes in Hank's buffer containing 1.4 mmol/L of calcium, 0.7 mmol/L of magnesium, and 10^{-6} mol/L of PMA. The cells were then centrifuged for 5 minutes at 240 *g*, resuspended in Hank's buffer, and immediately infused over 15 minutes. This activation procedure was repeated for a second aliquot of neutrophils while the first aliquot was being infused. Inactivated neutrophils were handled in an identical fashion apart from PMA activation.

Isolated Heart Preparation

Rabbits were anticoagulated with 500 units of heparin and anesthetized with 50 mg/kg of sodium pentobarbital administered through the marginal ear vein. After median sternotomy, the hearts were rapidly excised, mounted on a nonrecirculating Langendorff perfusion apparatus, and perfused with oxygenated (95% O_2–5% CO_2) Krebs-Henseleit solution (in mmol/L: NaCl, 118.3; KCl, 4.7; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; $CaCl_2$, 2.5; $MgSO_4$, 1.2; glucose, 10.0) at 37°C at a constant flow rate of 25 mL/min (Piper peristaltic pump model PL21T; Canlab, Mississauga, Ont, Canada). The glassware of the system was siliconized to prevent neutrophil adherence to the apparatus. Perfusion pressure, which directly reflects coronary vascular resistance in this constant-flow model, was monitored through a side-arm of the aortic cannula by means of a fluid-filled catheter connected to a pressure transducer. Contractile force was determined by means of a curved needle placed through the left ventricular apex and connected to a force-displacement transducer (Grass model FT03; Grass Instrument Co, Quincy, MA). Hearts were preloaded with a constant resting tension of 5.0 g. The rate of left ventricular tension development (dF/dt) and relaxation (−dF/dt) were determined electronically with a differentiator amplifier (Gould model 13-5615-71).

Experimental Protocol

After a 20-minute equilibration period, baseline determinations were obtained to establish that the preparation met acceptable hemodynamic criteria: absence of premature ventricular contractions, force development greater than 20 g, mean coronary perfusion pressure less than 50 mm Hg, and heart rate less than 200 beats/min. Preparations not meeting these criteria were not used. Studies were carried out in three groups on a randomized basis: control (C), unactivated neutrophil infusion (CN), and PMA-activated neutrophil infusion (AN). A total of 1.5×10^7 neutrophils was infused over 30 minutes (final concentration in the perfusate of 2×10^4/mL) through the side-arm of the aortic cannula via a Harvard infusion pump. Control hearts received an infusion of the suspending solution alone. Hearts were then arrested with a 3-minute infusion of modified St. Thomas' cardioplegic solution (in mmol/L: NaCl, 91.6; KCl, 25.0; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; $CaCl_2$, 0.6; $MgSO_4$, 1.2; $MgCl_2$, 15.0; glucose, 11.0) delivered at 4°C at an infusion rate of 21 mL/min. Hearts were then maintained in ischemic arrest at 20°C for 40 minutes before reperfusion for 30 minutes at 37°C. An additional infusion of cardioplegic solution for 3 minutes was given after the initial 20 minutes of ischemia. Hemodynamic variables were recorded at 15 and 30 minutes of the prearrest infusion period as well as every 10 minutes during the 30-minute postischemic reperfusion period. Left ventricular samples were then taken for determination of the presence of lipid peroxidation products and myocardial water content. Myocardial samples for water content were blotted dry, weighed, dried in an oven at 65°C for 24 hours, and then reweighed. Percent water content was equal to 1 − (dry weight/wet weight) × 100.

Lipid Peroxidation Determination

Myocardial biopsy specimens (150 mg) were homogenized in 0.85% saline solution and stored under nitrogen at −80°C. Conjugated diene, lipid soluble fluorescence, and sulfhydryl group content were determined spectrophotometrically as previously outlined [16]. Thiobarbituric acid–reactive material was assayed according to the method of Ohkawa and co-workers [17]. All lipid peroxidation determinations were adjusted based on the total protein content of the myocardial samples.

Statistical Analysis

All values are reported as mean ± standard error of the mean unless otherwise specified. Baseline hemodynamic function, lipid peroxidation determinations, and myocardial water content were compared by one-way analysis of variance followed by post hoc *t* tests. Hemodynamic function during the infusion and reperfusion periods was analyzed by one-way analysis of variance with post hoc comparisons at the last time point carried out using Tukey's test. A Bonferroni adjustment for multiple comparisons was used where applicable to maintain an overall significance level of $\alpha = 0.05$.

Results

Seven hearts were excluded from the study because of failure to meet baseline hemodynamic criteria. One heart assigned to the C group was excluded because of a force less than 20 g, 1 heart in the AN group because of a heart rate in excess of 200 beats/min, 1 heart in the C group and 1 heart in the AN group because of a coronary perfusion pressure greater than 50 mm Hg, and 2 hearts in the C group and 1 heart in the CN group because of persistent arrhythmias. The results are thus based on data obtained from 10 C, 5 CN, and 10 AN hearts. As outlined in Table 1, there were no significant differences among the groups with respect to baseline hemodynamic function.

Myocardial Function

There were no significant differences with regard to contractile force, dF/dt, −dF/dt, or coronary perfusion pressure between the C and CN groups, either during the prearrest infusion period or during the subsequent 30 minutes of reperfusion. Both groups showed initially depressed function after reperfusion with a gradual improvement to close to baseline levels in the ensuing 30 minutes. In contrast, there was a significant deterioration in contractile force during the activated neutrophil infusion (AN versus C; $p < 0.01$) (Fig 1). After reperfusion, the AN group showed an initial depression in force comparable with the two control groups. The control groups, however, subsequently showed recovery of function to a level similar to baseline whereas the AN group showed further deterioration (AN versus C, $p < 0.01$; AN versus CN, $p < 0.05$).

Activated neutrophils also affected both the rate of force development and the rate of relaxation such that there was a significant deterioration in both dF/dt and −dF/dt in the AN group. These effects are illustrated in Figures 2 and 3. Paralleling the changes in ventricular function, there was a progressive significant increase in the coronary resistance (Fig 4), both during the infusion period (AN versus C, $p < 0.05$; AN versus CN, $p < 0.01$) and during reperfusion (AN versus CN, $p < 0.05$).

Lipid Peroxidation

The results of the lipid peroxidation assays are presented in Table 2. There were no significant differences among the groups for any of the variables.

Myocardial Water Content

There were no significant differences among the groups with respect to myocardial water content. Mean values (± standard error) for each group were: C, 84.0% ± 0.13%; CN, 84.18% ± 0.23%; and AN, 83.95% ± 0.17%.

Table 1. Baseline Hemodynamic Function[a]

Group	Force (g)	Coronary Perfusion Pressure (mm Hg)	dF/dt (g/s)	−dF/dt (−g/s)
C	36.2 ± 1.9	37.7 ± 2.4	2,195 ± 118	2,275 ± 152
CN	36.7 ± 3.0	36.0 ± 2.1	2,340 ± 192	2,380 ± 214
AN	39.2 ± 2.3	43.3 ± 1.5	2,385 ± 144	2,545 ± 165

[a] Values are mean ± standard error. There are no significant differences among groups.

AN = activated neutrophil group; C = control group; CN = control (unactivated) neutrophil group; dF/dt = rate of left ventricular tension development; −dF/dt = rate of left ventricular relaxation.

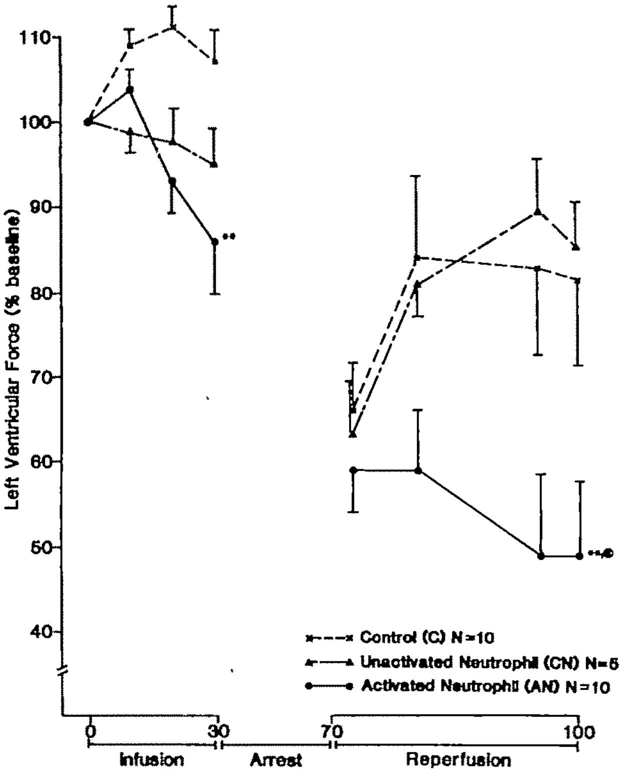

*Fig 1. Left ventricular force (as a percentage of baseline) during 30-minute neutrophil or control infusion and 30 minutes of reperfusion. (** AN versus C,* $p < 0.01$*; ⊛ AN versus CN,* $p < 0.05$*.)*

Comment

This study demonstrates significantly depressed recovery of function in rabbit hearts perfused with activated neutrophils before hypothermic ischemic arrest and subsequent normothermic reperfusion. Hearts perfused with nonactivated but otherwise identically isolated and prepared neutrophils exhibited significantly better recovery of function, which was no different from that seen in the crystalloid-perfused control group. The final concentration of neutrophils in the perfusate (2×10^4/mL) was considerably lower than the normal human (2.0 to 7.5 × 10^6/mL) or rabbit (3.2 to 9.5 × 10^6/mL) neutrophil count, emphasizing the potential physiologic significance of these findings. The study protocol may have further underestimated the role of activated neutrophils in this setting, as neutrophils were given only before ischemia and not during the reperfusion period.

There is a growing body of experimental evidence to demonstrate the importance of neutrophils in the pathophysiology of myocardial reperfusion injury. The role of the neutrophil as mediator of myocardial injury and dysfunction is of particular interest in cardiac surgery, as neutrophil activation has been shown to occur during

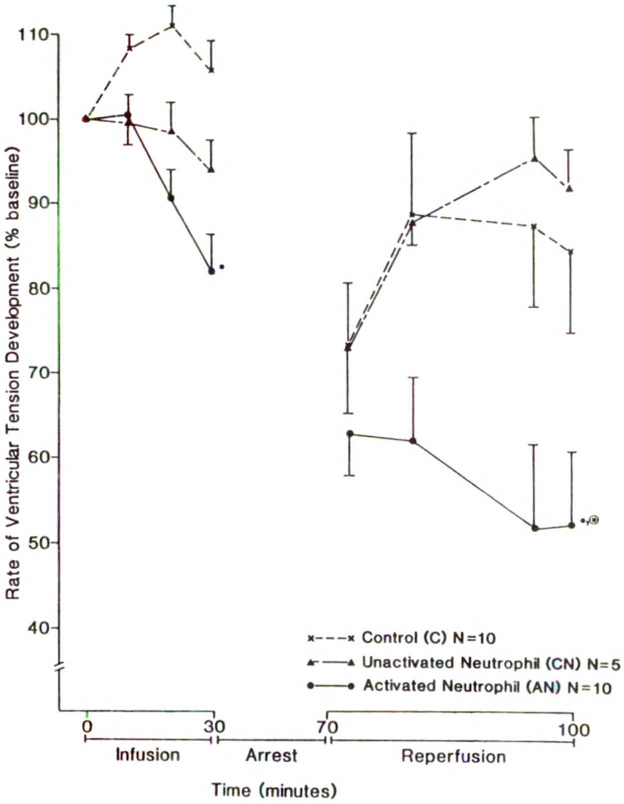

Fig 2. Rate of ventricular tension development (as a percentage of baseline) during 30-minute neutrophil or control infusion and 30 minutes of reperfusion. (AN versus C, $p < 0.05$; ⊛ AN versus CN, $p < 0.05$.)*

cardiac procedures via a number of mechanisms. Cardiopulmonary bypass has been clearly demonstrated to cause activation of the complement system [1–7]. C3a levels are significantly elevated within 10 minutes of the onset of bypass [1] and continue to rise thereafter to maximal concentrations of 10 to 16 times baseline at the time of sternal closure [7]. Blood trauma, as well as contact between blood and the foreign surfaces of the bypass circuit, particularly the oxygenator, appears to constitute one important source of complement activation. Although some investigators have demonstrated less complement activation with membrane as opposed to bubble oxygenators [3, 5], others have shown the opposite [7] or no difference between the two types [2, 6]. In vitro studies [18] have demonstrated that the protamine-heparin complex results in complement activation via the classic pathway, and subsequent clinical studies have confirmed this finding. Kirklin and associates [4] demonstrated highly significant increases in C3a, C4a, and C4d levels 5 minutes after protamine administration, and Cavarocchi and co-workers [3] found that the highest levels of C3a were those obtained 10 minutes after protamine administration.

Myocardial ischemia/reperfusion injury appears to constitute an additional source of complement activation. Hill and Ward [19] demonstrated that ischemic myocardium releases a protease capable of cleaving C3 into leukotactic fragments, and Pinckard and colleagues [20] demonstrated complement activation with acute myocardial ischemia in the baboon. More recently, it has been shown that canine cardiac lymph collected during reperfusion after 45 minutes of coronary occlusion contains subcellular components that can activate the complement cascade [9].

Complement activation factor C5a binds to neutrophil receptors and initiates a number of activation responses including chemotaxis, aggregation, microvascular endothelial adhesion, lysosomal enzyme release, and production of toxic oxygen metabolites including superoxide anion and hydrogen peroxide [3]. Patients undergoing cardiopulmonary bypass have been shown to have significantly elevated levels of myeloperoxidase and elastase as well as lactoferrin, which are released from neutrophil azurophilic and specific granules, respectively [8, 21]. Cavarocchi and associates [22] have demonstrated significantly increased levels of hydrogen peroxide in patients after bypass procedures.

Phorbol-12-myristate-13-acetate was used in this study to activate neutrophils. This agent appears to mimic the action of diacylglycerols, compounds normally formed from endogenous phospholipids during cell stimulation,

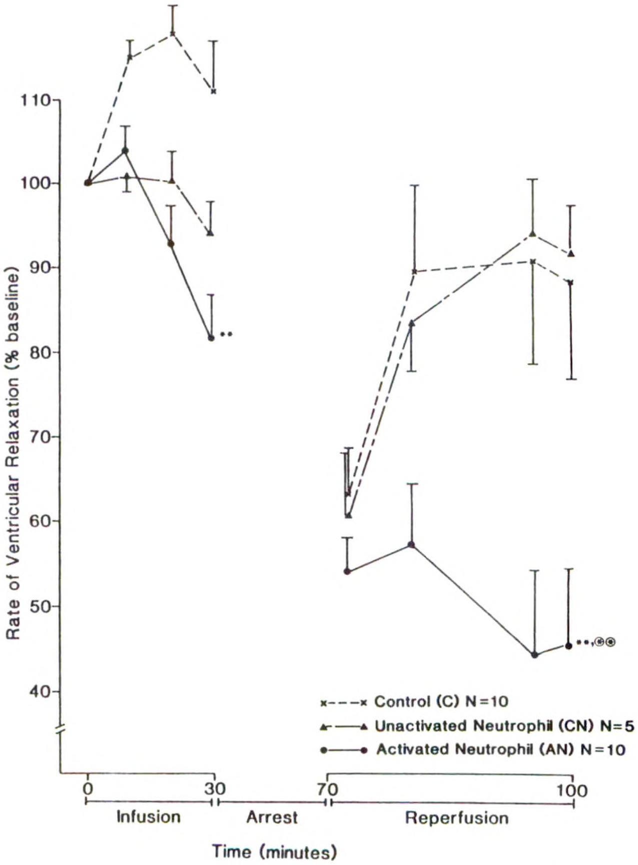

*Fig 3. Rate of ventricular relaxation (as a percentage of baseline) during 30-minute neutrophil or control infusion and 30 minutes of reperfusion. (** AN versus C, $p < 0.01$; ⊛⊛ AN versus CN, $p < 0.01$.)*

and has been shown to stimulate both neutrophil degranulation [23] and the production of reactive oxygen metabolites [24]. Initial pilot studies suggested that infusion of PMA alone could result in some degree of myocardial depression, a finding that is not entirely surprising in view of its known ability to activate protein kinase C [25]. This potentially confounding factor was eliminated from the present study by resuspension of activated neutrophils in PMA-free medium before infusion.

There are a number of mechanisms whereby neutrophils may cause myocardial damage and dysfunction including the release of leukotrienes, platelet-activating factor, proteolytic enzymes, and toxic oxygen metabolites. There is now extensive evidence to suggest that oxygen radicals and their metabolites are important mediators of myocardial reperfusion injury [26]. Much of this tissue injury occurs secondary to lipid peroxidation of the polyunsaturated fatty acids found in cellular and subcellular membranes. Left ventricular biopsy specimens obtained at the end of each study were analyzed using several techniques to detect lipid peroxidation, but there were no detectable differences among the groups. Thus, lipid peroxidation may not be an important mechanism of injury in this model. Alternatively, as it is expected that the injury would be primarily at the level of the endothelial cell rather than the myocyte, the negative results reported here may simply reflect the limited sensitivity of the available assays in view of the large number of myocytes versus endothelial cells in the myocardial tissue samples. In addition, it is possible that the necessary delay in obtaining the biopsy specimens until the end of the reperfusion period may have missed the maximal peroxidative effect.

Table 2. Lipid Peroxidation Determinations[a]

Variable	C	CN	AN
Conjugated dienes (nmol/mg)	178 ± 14	214 ± 19	220 ± 14
Lipid-soluble fluorescence (%/mg)	6.4 ± 1.6	3.2 ± 0.6	5.1 ± 1.6
Sulfhydryl group content (nmol/mg)	38.0 ± 2.7	36.2 ± 3.6	45.1 ± 3.1
Thiobarbituric acid–reactive material (ng/mg)	266 ± 29	182 ± 39	219 ± 30

[a] Values are mean ± standard error. No significant differences among groups.

AN = activated neutrophil group; C = control group; CN = control (unactivated) neutrophil group.

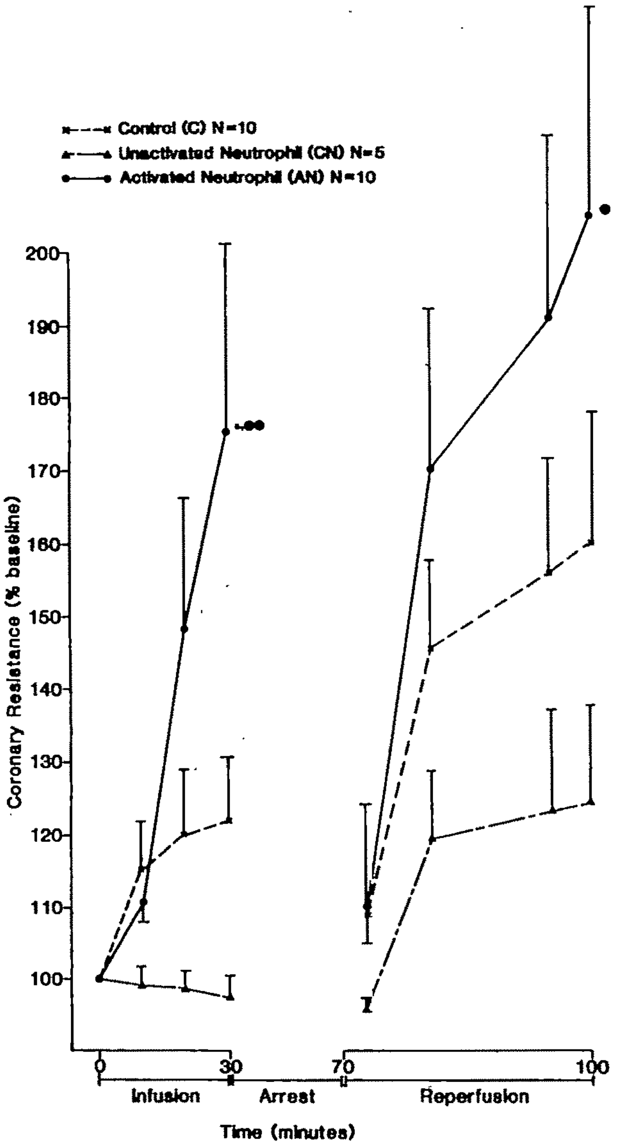

Fig 4. *Coronary resistance (as a percentage of baseline) during 30-minute neutrophil or control infusion and 30 minutes of reperfusion. (* AN versus C,* $p < 0.05$*; ⊛⊛ AN versus CN,* $p < 0.01$*; ⊛ AN versus CN,* $p < 0.05$*.)*

Neutrophil-mediated myocardial dysfunction may also occur secondary to microvascular plugging with resulting heterogeneous perfusion and secondary cellular ischemia [27]. Leukocytes are larger and less compliant than erythrocytes and thus have more difficulty in traversing the microvasculature. Hypoxic endothelial cell injury has been shown to increase neutrophil adherence [28], as has complement-induced neutrophil activation [3]. Engler and co-workers [29] examined the effect of neutrophil depletion in a canine model of 1 hour of coronary artery occlusion followed by reperfusion. In addition to significant decreases in ventricular arrhythmias and myocardial edema, a dramatic reduction in the no-reflow phenomenon was demonstrated in neutrophil-depleted animals. Release of mediators from adherent and activated neutrophils may also contribute to impaired microvascular reperfusion. Studies using isolated canine [30] and rabbit [31] arterial rings have shown that neutrophils can invoke sustained, concentration-dependent vascular constriction. The significant increase in coronary resistance seen in this study in the hearts receiving activated neutrophils suggests the potential importance of these mechanisms.

In conclusion, this study demonstrates significantly compromised recovery of function in rabbit hearts perfused with activated neutrophils before hypothermic ischemic arrest and subsequent normothermic reperfusion. Further investigation is required to elucidate the pathophysiologic mechanisms involved. Although extrapolation of in vitro experimental animal data to humans must be done with great caution, this would appear to be of relevance to cardiac operations, wherein both neutrophil activation and myocardial ischemia occur.

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Methods of Implantable Cardioverter-Defibrillator–Pacemaker Insertion to Avoid Interactions

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Experience with combined transvenous pacemaker and implantable cardioverter-defibrillator insertion in 21 patients is described. Special techniques are needed to avoid potentially lethal pacemaker–implantable cardioverter-defibrillator interaction. Separation between leads for the two devices should be maximized. The electrophysiologic criteria for successful device function can be met, even when some leads for both devices must be placed by a transvenous approach.

(Ann Thorac Surg 1992;53:253–7)

Implantable cardioverter-defibrillators (ICDs) markedly reduce arrhythmic death in survivors of cardiac arrest [1–3]. Because the majority of patients who are candidates for ICD implantation suffer from advanced heart disease [1, 2], some patients who undergo ICD implantation will also require permanent pacemakers for sinus bradycardia, sinus arrest, or atrioventricular block [4, 5]. The indication for an ICD or pacemaker may also be discovered after one or the other has already been implanted. Maximum safety is promoted in combined implantation by making pacemaker output invisible to the ICD, thereby avoiding inappropriate ICD discharges and failure of the ICD to recognize and respond to ventricular fibrillation. We describe methods that we have found useful in achieving this goal.

Material and Methods

We have previously described our approach to ICD implantation [6]. These patients are generally, but not always [2, 3], survivors of cardiac arrest in whom antiarrhythmic drugs are ineffective, poorly tolerated, or untestable. The need for transvenous pacing may be discovered in the course of electrophysiologic testing for ICD implantation. Some patients who are candidates for an ICD will have previously undergone pacemaker insertion. Other patients will be discovered to need a pacemaker after ICD insertion. The technique described here is best suited for patients undergoing ICD insertion through a left thoracotomy without simultaneous coronary bypass grafting.

General anesthesia, maintenance of heart rate with drugs or temporary pacing, excellent fluoroscopy, and electrocardiographic monitoring are essential. Adhesive external defibrillation electrodes are applied to the anterior right chest and posterolateral left chest. A fluoroscopy table must be used, and careful positioning is required to allow successful fluoroscopy and left thoracotomy in the presence of adhesive external defibrillation electrodes. We begin with a standard approach to transvenous pacing, exposing a cephalic or other small venous branch through a 3- to 4-cm incision beneath the left clavicle. Pacing wires are introduced directly through a small venotomy or through a 7F strip-away percutaneous catheter introducer (No. 405108; Daig Corp, Minnetonka, MN) passed over a small guidewire. Fluoroscopy is then used to insert ventricular or atrial pacing wires as needed. The pacemaker system must be bipolar [7]. For ventricular pacing, we prefer two unipolar, positive fixation, screw-in permanent pacing electrodes (Model 435-02; Intermedics, Inc, Freeport, TX) positioned close together in the outflow tract of the right ventricle (RV) or in the anterior RV, just across the tricuspid valve (Figs 1, 2).

Adequacy of sensing and pacing thresholds is confirmed before installing the pacemaker generator. A pacemaker system analyzer is used to determine thresholds for each unipolar lead, seeking pacing thresholds of less than 0.7 V, an R wave greater than 5 mV, and impedance of approximately 500 Ω. The leads are then tested in the bipolar configuration, usually providing pacing thresholds and R-wave amplitude similar to the unipolar configuration, except that bipolar impedance is about 1,000 Ω. Both possible bipolar polarities are tested, and the configuration giving the lower pacing threshold is identified with a marking tie on the negative lead. The leads are connected to a bipolar pacing generator. An adapter is usually required for these connections, because most current pacemakers use in-line bipolar connectors. Y adapters (5 mm to vs-1 or is-1) are available from Medtronic, CPI, Telectronics, and other manufacturers. Similar techniques of insertion, testing, and connection of paired atrial leads are employed when atrial or dual

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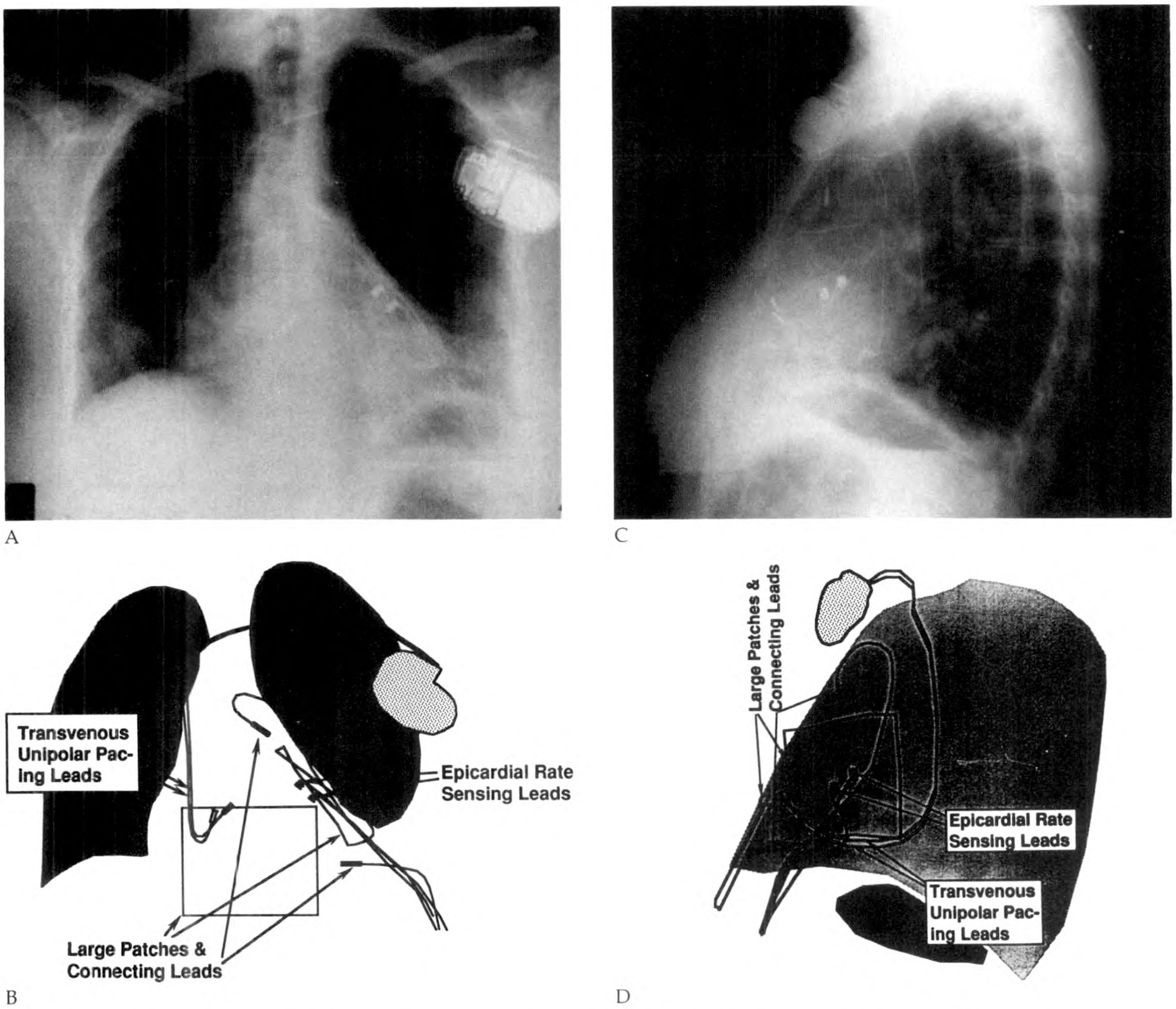
A
C
Transvenous Unipolar Pacing Leads
Epicardial Rate Sensing Leads
Large Patches & Connecting Leads
B
Large Patches & Connecting Leads
Epicardial Rate Sensing Leads
Transvenous Unipolar Pacing Leads
D

Fig 1. Posteroanterior (A) and lateral (C) roentgenograms reveal transvenous bipolar VVI pacemaker and epicardial ICD inserted by left thoracotomy in a 56-year-old woman. Schematic diagrams (B, D) identify two positive-fixation pacemaker leads in the right ventricle, two myocardial ICD rate-sensing leads, and two large extrapericardial patch leads.

chamber pacing is indicated. Leads are placed in the atrial appendage or lateral right atrium as required.

A left anterolateral thoracotomy incision is then performed, usually excising a small (7 cm) segment of the fifth rib. Intrapericardial/myocardial rate-sensing electrodes and extrapericardial large patch electrodes for the ICD are installed. Alternatively, the rate-sensing leads and a spring-coil defibrillator lead may be inserted through the subclavian vein (see Fig 2). During transvenous pacing at maximum pacemaker output and pulse width, the electrograms in both the rate-sensing and morphology leads are examined to confirm that pacemaker spikes are less than 0.2 mV in amplitude or less than 5% of the QRS amplitude in the rate-sensing leads. If these criteria are not met, either the pacemaker or ICD leads are repositioned (Fig 3).

After lead positioning, cardioversion thresholds are measured by our electrophysiologists (J.T.B., J.S.S., F.L.) in ventricular tachycardia (when inducible) and in ventricular fibrillation, with transesophageal or epicardial echocardiographic monitoring of wall motion and ejection fraction when possible, as we have described previously [4]. Defibrillation thresholds are measured with an external cardioverter defibrillator (CPI) and must be 20 J or less. External defibrillator backup and availability of internal paddles can be critical if thresholds are unexpectedly high. Implantable cardioverter-defibrillator lead configurations are adjusted until defibrillation thresholds are adequate.

A hemostatic, abdominal subcutaneous pocket is fashioned through a left upper quadrant incision. The ICD leads are tunneled through the diaphragm and attached

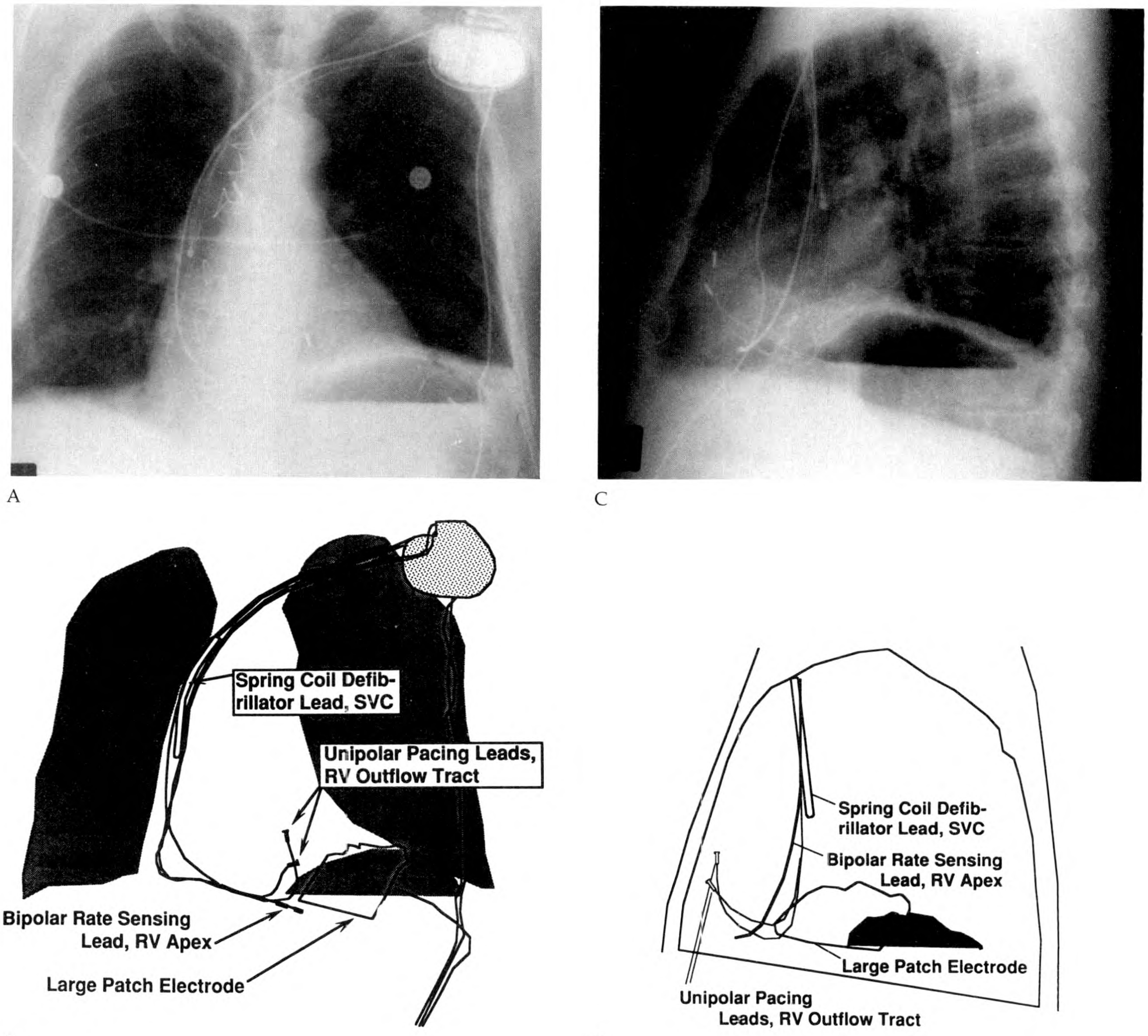
A
C
Spring Coil Defibrillator Lead, SVC
Unipolar Pacing Leads, RV Outflow Tract
Bipolar Rate Sensing Lead, RV Apex
Large Patch Electrode
B
Spring Coil Defibrillator Lead, SVC
Bipolar Rate Sensing Lead, RV Apex
Large Patch Electrode
Unipolar Pacing Leads, RV Outflow Tract
D

Fig 2. Posteroanterior (A) and lateral (C) roentgenograms reveal transvenous bipolar VVI pacemaker and ICD in a 60-year-old man with previous coronary artery bypass grafting. Schematic diagrams (B, D) identify leads. Two positive-fixation pacemaker leads are visible in the right ventricular outflow tract. Technical considerations led also to transvenous insertion of an endocardial, bipolar rate-sensing lead and a spring-coil defibrillator lead in the superior vena cava. One large patch was inserted in an extrapericardial location through a left thoracotomy. Successful function of this lead configuration is illustrated in Figure 4. (RV = *right ventricular;* SVC = *superior vena cava.)*

to the ICD, which is activated and tested. Our experience encompasses AICD models AID-B (Intek) and Ventak models 1510, 1520, 1550, and 1600 (CPI). The most stringent test is successful ICD detection and cardioversion from ventricular fibrillation during magnet-forced asynchronous ventricular or asynchronous atrioventricular pacing at maximum pacemaker output and pulse width (Fig 4). The absence of double counting of pacing spikes and QRS complex during asynchronous ventricular or asynchronous atrioventricular pacing should also be confirmed by listening to the R-wave synchronous tones emitted when a magnet is applied to an activated ICD. Finally, the ICD is temporarily inactivated and all incisions are closed, incorporating a small left chest tube. The patient is generally awakened and extubated in the operating room. Epidural fentanyl analgesia is administered in the intensive care unit for 24 to 48 hours. All devices are again tested in the electrophysiology laboratory 1 week postoperatively before discharge.

Results

Our clinical experience includes 114 ICD system insertions since 1984, with one infarction-related perioperative

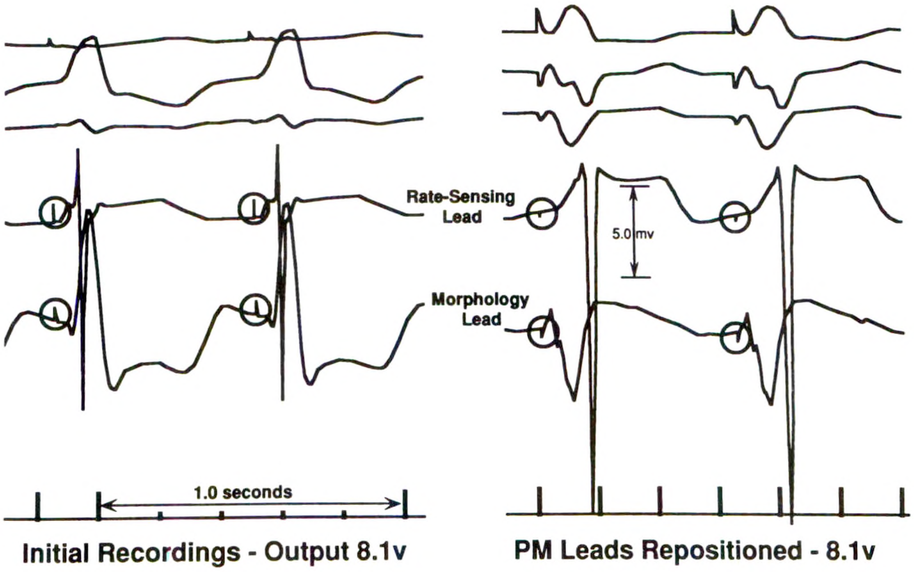
Rate-Sensing Lead
Morphology Lead
5.0 mv
1.0 seconds
Initial Recordings - Output 8.1v
PM Leads Repositioned - 8.1v

Fig 3. The pacing spikes illustrated in the left panel were judged unacceptably large in the rate-sensing leads. After repositioning, as shown on the right, the pacemaker spikes decreased in size, the amplitude of the native QRS increased, and the lead position was considered adequate.

mortality. At mean follow-up of 2.9 years, only one arrhythmic death may have occurred. Twenty-one of these patients have required ICDs in combination with pacemakers (19) or pacing leads (2). Pacemakers implanted consisted of 12 VVI, 6 DDD, and one antitachycardia pacemaker. In 3 patients, the need for transvenous pacing was established and pacemaker insertion occurred weeks or months after ICD insertion. In 12 patients, ICD implantation was combined with pacemaker insertion (10) or lead insertion only (2) using the methods described. Five additional patients were referred for ICD insertion with previously inserted pacemakers; in 2 of these patients (DDD) satisfactory function of both devices was achieved by moving the ICD rate-sensing leads as far as possible to the posterolateral aspect of the left ventricle. The remaining 3 patients required new transvenous leads and testing, as described in the Material and Methods section.

Overall, we found it necessary to reposition or replace ventricular pacemaker leads four times—twice from the RV apex to the outflow tract and twice from outflow tract to the anterior RV, close to the tricuspid valve. In 1 patient with DDD pacing and chronically implanted unipolar leads in the right atrial appendage and RV apex, successful conversion to bipolar pacing was accomplished by placing a second unipolar lead close to the chronic leads and proceeding as described. We have found that either RV or right atrial pacing wires can cause interactions with ICDs. Accordingly, both lead systems must be individually tested.

Comment

The methods and testing described here were not used in one patient, our first pacemaker recipient, who received a bipolar DDD pacemaker. That patient is the only one in

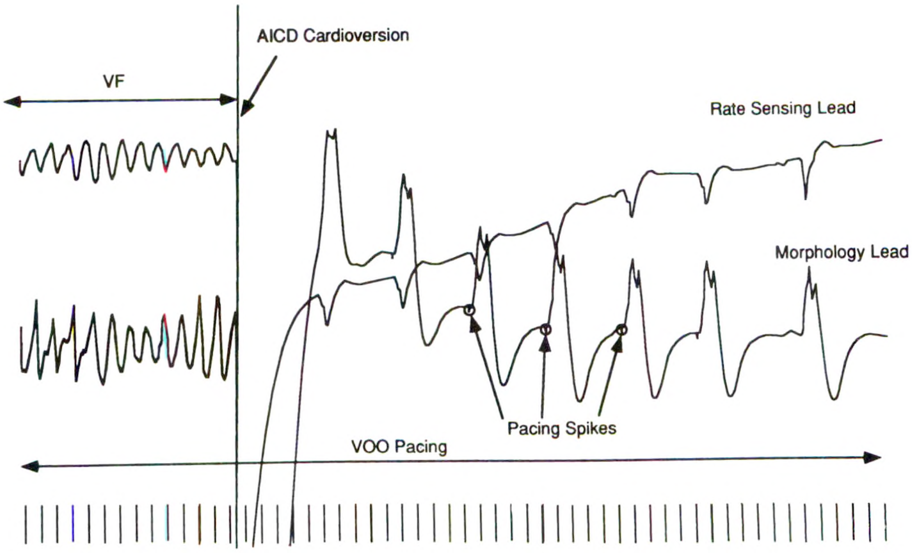

*Fig 4. Successful test of leads illustrated in Figure 2. Continuous right ventricular bipolar pacing is forced by a magnet applied to the pacemaker. The pacing spikes do not prevent detection and cardioversion by the ICD. The pacing spikes are invisible except in the bipolar "morphology lead" (patch and superior vena cava electrodes), where they measure less than 0.4 mV. (*AICD = *automatic implantable cardioverter-defibrillator;* VF = *ventricular fibrillation;* VOO = *asynchronous ventricular.)*

our series of 114 ICD recipients who may have suffered arrhythmic death. The circumstances of that event are not fully known, as the patient died while sleeping alone, at home. Nevertheless, that experience leads us to recommend that all steps to avoid pacemaker-ICD interaction be followed stringently.

Pacemaker-ICD interaction can cause either unnecessary ICD discharges or inappropriate ICD inhibition permitting sudden death [3]. Unnecessary ICD discharges can occur if the highly sensitive circuits of the ICD detect both the pacing spike and the QRS depolarization in VVI pacing (double counting). Similarly, triple counting can occur (atrial spike, ventricular spike, and QRS) in DDD or DVI pacing. In both cases, a paced rate of 90 beats/min will exceed the common ICD rate cutoff of 173 and lead to ICD firing [8].

More ominous is the potential problem in ventricular fibrillation. Ventricular fibrillation may not inhibit ventricular pacing [4]. The ICD may not detect ventricular fibrillation in the presence of unipolar ventricular pacing spikes if the amplitude of the pacing spikes substantially exceeds the low amplitude of the waves of ventricular fibrillation. The ICD thus may interpret pacemaker spikes as a normal ventricular rhythm, a phenomenon that has been observed in patients [4].

Other adverse ICD-pacemaker experiences described in the literature include potentially lethal reciprocal triggering of an ICD and antitachycardia pacemaker [8], inadvertent induction of ventricular tachycardia triggered by an "R on T" phenomenon during a pacemaker magnet test [8] or burst pacing [9], and transient sensing and pacing dysfunction of transvenous pacemakers after ICD discharges [4]. Many of these problems will be eliminated when devices integrating ICD and pacemaker functions in a single unit are released, hopefully within 2 to 3 years.

Many difficulties of ICD-pacemaker interaction can be avoided with present, independent devices by making the pacemaker signals invisible to the ICD. Unipolar pacing is contraindicated in this setting because of the large pacing spikes generated [7]. Recently, it has been recommended that pacemakers implanted in ICD recipients should be capable of function only in the bipolar mode, because pacemakers capable of function in the unipolar mode could be inadvertently programmed to the unipolar mode or may use that mode as an indicator of battery depletion.

The optimal lead configuration consists of bipolar RV endocardial pacing electrodes and bipolar left ventricular epicardial ICD electrodes. In-line bipolar pacemaker leads can be useful but are stiff in comparison with unipolar leads and, as we have observed, may not provide good R-wave amplitude in the outflow tract. The increased flexibility of unipolar positive-fixation leads promotes stability of pacemaker leads in locations such as the RV outflow tract and anterior RV, which we prefer. We have observed no displacement of more than 30 leads implanted in these locations with the technique and lead described. Others have also described successful experiences with outflow tract pacing [10]. We have found moving the epicardial rate-sensing leads, described by others [8], useful to minimize ICD-pacemaker interaction. But we find the ability to move twin unipolar leads widely within the RV to be even more useful. This has even allowed endocardial ICD rate-sensing leads and pacemaker leads to be combined (see Fig 2). Successful operation of this lead configuration is illustrated in Figure 3.

In summary, the need for simultaneous insertion of both an ICD and a permanent pacemaker is a problem created in part by delayed development of a single device capable of both functions. The techniques must be well understood, because bradycardic death in ICD recipients has been reported [5]. However, even when dual-function devices become available, special situations will arise that require familiarity with the techniques described. Detection of pacemaker spikes by the ICD can lead to either inappropriate ICD discharges or failure of the ICD to detect and fire in ventricular fibrillation. These problems can be avoided by use of bipolar pacemakers and lead configurations physically separating the lead systems.

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Twenty-Year Follow-up of Saphenous Vein Aortocoronary Artery Bypass Grafting

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The clinical records of our first 100 patients to undergo saphenous vein aortocoronary bypass grafting were reviewed. The procedures were performed between March 19, 1970, and March 30, 1972. The patient population included 84 men, and the mean age was 51.4 years. There were 12 patients with single-vessel disease, 36 with double-vessel disease, and 52 with triple-vessel disease, for an average of 2.4 involved vessels per patient. Forty-eight patients were judged to have diffuse atherosclerotic disease. Twelve patients had left main coronary artery stenoses. Each patient received an average of 1.8 saphenous vein grafts. Thirty-six patients underwent repeat coronary artery bypass grafting after an average of 132.8 months and received an average of 3.5 grafts. This resulted in cumulative reoperative rates of 5%, 14%, 27%, and 36% at 5, 10, 15, and 20 years, respectively. The 5-, 10-, 15-, and 20-year survival rates were 89.8%, 68.4%, 53.1%, and 40.8%, respectively. Survival was not significantly related to the cause of death, cardiac-related causes being predominant. There were no significant relationships between the length of survival and sex, the number of grafts received, or the presence of left main stenosis. Survival was inversely related to age at initial operation ($p = 0.046$) as well as initial left ventricular end-diastolic pressure ($p = 0.033$). Survival positively correlated with the occurrence of triple-vessel disease ($p = 0.031$) and the presence of diffuse disease ($p = 0.0077$). Survival correlated with the occurrence of repeat grafting ($p = 0.0079$), the interval to repeat grafting ($p = 0.0001$), and survival after repeat grafting ($p = 0.030$), but again did not correlate with the operation received. The 5- and 10-year survival rates for repeat operation were 77.4% and 71.0%, respectively. Saphenous vein coronary artery bypass grafting in this era yielded a 41% 20-year survival. Cardiac-related events continued to account for the majority of all late deaths. Thirty-six percent of all patients and 53% of all long-term survivors underwent repeat operation. Repeat operation significantly influenced long-term survival.

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Since the initial report by Favaloro [1], aortocoronary artery bypass grafting (CABG) has become commonplace. A vast body of literature is available regarding the risks, benefits, and long-term survival. Much has changed since the early days of this operation with improvements in surgical technique, lighting, magnification, suture material, cardiopulmonary bypass techniques, and myocardial protection. The use of arterial conduits, such as the internal mammary artery [2, 3] and more recently the right gastroepiploic artery [4], has been shown to improve graft patency rates. In contrast to the 40% to 60% patency rate for vein grafts at 10 to 12 years postoperatively, arterial graft patency exceeds 90% [2].

Several articles have been published regarding the 5-year [5–10], 10-year [3, 5–14], and even 15-year [15, 16] survival rates after CABG. Factors determining survival are controversial. Age [8, 11, 13, 15], sex [6], left ventricular function [5, 7, 8, 12, 13, 15], severity of coronary artery disease [7, 12, 15], left main coronary disease [8], the number of grafts received [6], associated left ventricular aneurysmectomy [6], completeness of revascularization [7, 12], previous revascularization [15], diabetes mellitus [16], and hypertension [8] have been suggested as significantly affecting long-term survival. In this report, we present the 20-year survival data for our earliest group of CABG patients.

Material and Methods

Patient Population

The clinical records of the first 100 patients to undergo CABG by our group were reviewed. The procedures were performed between March 19, 1970, and March 30, 1972. The patient population consisted of 84 men and 16 women with a mean age (± standard error of the mean) of 51.4 ± 1.5 years (range, 36 to 64 years). Most patients underwent operation for crescendo or disabling angina pectoris.

The mean left ventricular end-diastolic pressure (LVEDP) was 16.6 ± 1.9 mm Hg (range, 5 to 39 mm Hg). The left ventricular ejection fraction was not quantitated in the initial catheterizations, and films were not available for review. Lesions were considered critical if they occluded greater than 70% of the luminal cross-sectional area. There were 12 patients with single-vessel disease, 36 with double-vessel disease, and 52 with triple-vessel disease, for an average of 2.4 ± 0.1 involved vessels per patient. Forty-eight patients were judged to have diffuse

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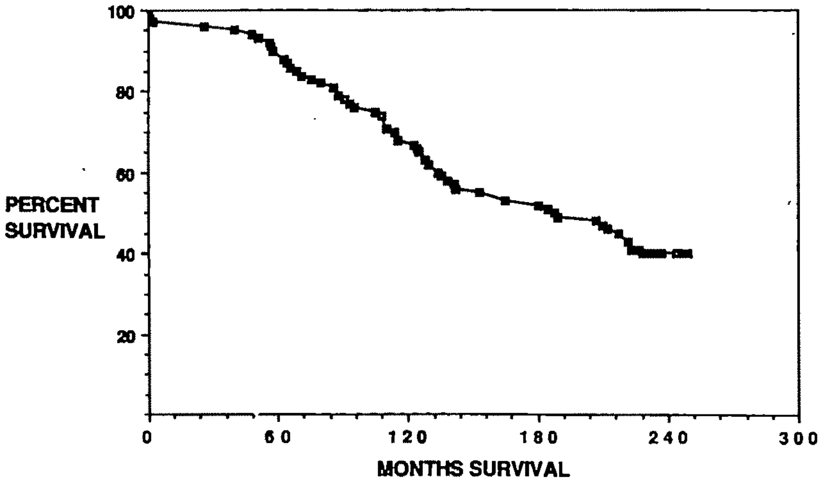

Fig 1. Kaplan-Meier survival curve for the 100 patients undergoing primary coronary artery bypass grafting.

disease, defined as greater than 50% cross-sectional luminal atherosclerotic involvement of 50% or more of the vessel length. Twelve patients had left main coronary artery stenoses. The patients received an average of 1.8 ± 0.1 saphenous vein grafts (range, 1 to 3 grafts). In addition, 10% of patients received either one (n = 6) or two (n = 4) internal mammary artery–left ventricular myocardial implants (Vineberg procedure).

Thirty-six patients underwent repeat CABG after an average of 132.8 ± 9.4 months (range, 21 to 223 months) and received an average of 3.5 ± 0.3 grafts (range, 2 to 5 grafts). Three of the patients received four internal mammary artery grafts. This resulted in cumulative reoperative rates of 5%, 14%, 27%, and 36% at 5, 10, 15, and 20 years, respectively. The average age of these 36 patients was 50.4 ± 2.1 years (range, 36 to 61 years) at the time of the initial operation. Twenty-nine (80.6%) were men. The initial LVEDP of this group averaged 18.2 ± 3.0 mm Hg (range, 7 to 33 mm Hg). Twenty-nine patients (80.6%) had diffuse disease on initial catheterization and had involvement of an average of 2.7 ± 0.2 vessels, although these patients received an average of 1.7 ± 0.1 grafts at the initial procedure.

Two patients underwent a second repeat CABG an average of 214.5 ± 4.5 months after the initial procedure (210 and 219 months). Four patients underwent percutaneous transluminal coronary angioplasty of either a graft or native vessel an average of 187.5 ± 15.2 months (range, 151 to 225 months) after the initial procedure.

Statistical Analysis

Data were analyzed by Student's t test (two-tailed), Mann-Whitney U test, and multiple regression analysis where appropriate. Survival was determined by actuarial analysis using the methods of Kaplan and Meier [17, 18], with the day of operation as the starting time. Differences resulting in a p value of less than 0.05 were considered significant.

Results

Follow-up, conducted by telephone interview and review of all medical records, was current for all patients. It averaged 161.1 ± 7.5 months (range, 1 to 249 months) and equaled 1,342.5 patient-years. Of the 100 patients, 40 are currently alive.

There were seven perioperative deaths, defined as death within 30 days of operation or within the same hospitalization. Two occurred after the initial operation (one, pulmonary embolism, and one, cardiac related), and five occurred after repeat CABG (13.9%, 5/36) (3, cardiac related; 1, cerebrovascular accident; and 1, septic shock). For the entire patient population, the mean survival after primary operation, exclusive of perioperative deaths, was 164.0 ± 7.2 months (range, 1 to 249 months). The 5-, 10-, 15-, and 20-year survival rates were 89.8%, 68.4%, 53.1%, and 40.8%, respectively (Fig 1).

Length of survival was not significantly related to the cause of death. Stratification by years after operation demonstrated no significant difference in causes of death between early and late postoperative periods (Table 1). Cardiac-related deaths predominate in both early and late postoperative intervals. Survival was inversely related to age at initial operation ($p = 0.046$). The mean age at initial operation was 45.6 ± 3.0 years for patients currently alive compared with 52.8 ± 1.5 years for patients who have died. Female patients lived an average of 183.2 ± 14.7 months compared with 156.9 ± 8.4 months for male patients ($p = 0.20$).

Table 1. Causes of the 60 Deaths Grouped by 5-Year Intervals[a]

	Postoperative Years			
Variable	1–5	6–10	11–15	6–20
No. of deaths	11	22	16	11
Cause of death				
Perioperative	2 (18.2)	1 (4.5)	3 (18.8)	1 (9.1)
Cardiac related	7 (63.6)	12 (54.5)	9 (56.3)	7 (63.6)
Cancer	1 (9.1)	5 (22.7)	2 (12.5)	2 (18.2)
Vascular	1 (9.1)	2 (9.1)	. . .	. . .
Infection	. . .	1 (4.5)	2 (12.5)	. . .
Other	. . .	1 (4.5)	. . .	1 (9.1)

[a] Numbers in parentheses are percentages.

Table 2. Comparison of Survival by Severity of Disease

Variable	Percent Survival 5-Year	10-Year	15-Year	20-Year	Mean Survival[a] (mo)	Range (mo)
Vessels involved						
One	100	33	0	0	119.3 ± 23.4	88–165
Two	66.7	33.3	22.2	0	102.4 ± 27.4	1–223
Three	100	69.2	46.1	38.5	167.7 ± 19.5	63–249
Disease						
Diffuse	91.7	75.0	50.0	41.7	182.0 ± 19.8	93–249
Nondiffuse	84.6	30.8	15.4	0	104.0 ± 17.5	1–223
Left main						
Involved	100	33.3	0	0	99.7 ± 19.2	63–128
Not involved	86.4	54.6	36.5	22.7	145.6 ± 16.9	1–249

[a] Data are shown ± the standard error of the mean.

Curiously, there was a significant positive relationship between survival and initial LVEDP ($p = 0.033$). The initial mean LVEDP was 23.8 ± 3.2 mm Hg for patients who are alive compared with 14.4 ± 2.0 mm Hg for those who have died. All 12 patients with left main coronary stenoses have died ($p = 0.38$). Patients with left main coronary stenoses had involvement of an average of 2.7 ± 0.3 vessels compared with an average of 2.4 ± 0.2 vessels for patients without left main disease. Survival was also strongly positively correlated with the presence of diffuse disease ($p = 0.0077$) on initial catheterization. For patients with diffuse coronary artery disease, an average of 2.9 ± 0.1 vessels were involved. This was in contrast to an average of 1.9 ± 0.2 involved vessels in patients without diffuse disease. Survival positively correlated with the occurrence of triple-vessel disease ($p = 0.031$). All patients currently alive (n = 40) had diffuse triple-vessel disease on initial catheterization compared with only 35% (n = 21) of those who have died (Table 2). Patients still alive had an average of 2.9 ± 0.1 vessels involved compared with 2.3 ± 0.2 vessels for those who have died ($p = 0.031$). Those living received an average of 1.6 ± 0.3 grafts at the initial operation compared with 1.9 ± 0.1 grafts for those who have died ($p = 0.48$).

After repeat CABG, the mean survival was 62.3 ± 8.1 months (range, 1 to 166 months), with 21 patients (58.3%) currently alive (Fig 2). The 5- and 10-year survival rates for repeat operation were 77.4% and 71.0%, respectively. The mean survival after the second repeat operation is 12.0 ± 5.0 months (7 and 17 months) and after percutaneous transluminal coronary angioplasty, 39.5 ± 12.6 months (range, 7 to 67 months), with all 6 patients currently alive.

Survival correlated with the occurrence of repeat CABG ($p = 0.0079$), the interval to repeat CABG ($p = 0.0001$), and survival after repeat grafting ($p = 0.030$), but again did not correlate with the operation received ($p = 0.50$). Repeat grafting was performed later (mean interval, 161.4 ± 9.7 months after the initial procedure) in the 21 patients currently alive than in the 15 patients who have died (mean interval, 92.9 ± 12.1 months). Those dying lived an average of 40.1 ± 13.0 months after repeat grafting compared with 66.3 ± 9.4 months for those still alive. For the 36 patients undergoing repeat CABG, the causes of death included 5 perioperative deaths (33.3%), 8 late cardiac-related deaths (53.3%), and 1 death each from lung cancer and Legionnaires' disease. Cardiac-related deaths after repeat CABG typically occurred within the first 5 postoperative years ($p = 0.015$).

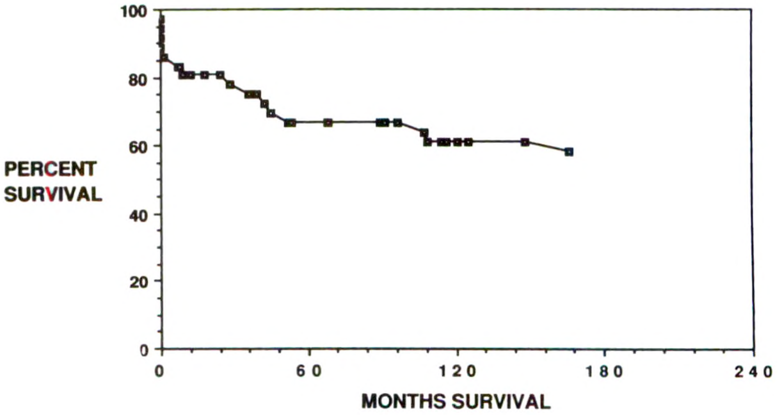

Fig 2. Kaplan-Meier survival curve for the 36 patients undergoing repeat coronary artery bypass grafting.

Comment

This study records the follow-up of our earliest group of CABG patients, the first of whom we saw more than 20 years ago. The longest reported follow-up to date has been 10 to 15 years [5, 7, 8, 12]. To accurately compare the results of different studies, several variables must be equivalent. The era in which operations were performed should be considered, as numerous technological and procedural advances have taken place in the ensuing years and have undoubtedly influenced survival. Vascular anastomosis has evolved from the use of fine silk into the use of atraumatic monofilament suture. No longer is intermittent vessel occlusion needed. Cardioplegia has allowed the grafting of a larger number of smaller-caliber vessels in a motionless field while concomitantly protecting the myocardium in the distribution at risk. This time frame, with respect to operation, has been shown to affect both in-hospital and late mortality [6]. The period 1970 to 1972 in this report is inclusive within some studies [8, 12, 16] and at the beginning of others [5, 9, 10, 14].

Series should also be equivalent in terms of perioperative mortality, age, sex, left ventricular function, vessel involvement, and number of grafts received. In the current study, a perioperative mortality of 2% at primary operation is similar to that reported by several authors (1.6% to 4.5%) [6, 9, 11–14]. The mean age of 51.4 years reported here compares well with that of other investigations of this era [6, 11, 13]. Also, as reported by others [5, 8, 13, 15], age significantly influenced long-term survival. Although the majority (84%) of patients in this and other series (84% to 89%) were male [6, 11, 13], sex did not affect long-term survival. Male and female patients of comparable ages had virtually identical 10-year and 15-year survival rates in a study by Johnson and associates [15].

An increase in LVEDP, which should reflect diminished left ventricular ejection fraction, positively correlated with an increased survival. Patients currently alive had a mean LVEDP of 23.8 mm Hg compared with a mean of 14.4 mm Hg for those who have died. Pirk and associates [7] showed that long-term survival did not correlate with left ventricular ejection fraction, which contradicts the findings of the majority of previous studies [8, 12–15].

The incidence of left main coronary artery disease was similar to that previously reported [11]. Although the result was not significant, probably because of the small number of patients in the current study, all patients with left main coronary stenoses have died. Rowe and colleagues [6] and Lytle and associates [8] showed that both hospital mortality and long-term survival were significantly related to the presence of critical left main coronary disease.

The proportion of patients with single-vessel disease (12%) compares well with a study by Coll Mazzei and colleagues [13], although it is far less than the 38.6% reported by Adams' group [12]. The proportions of patients with double-vessel (36%) and triple-vessel disease (52%) are similar as well (43.7% and 48%, respectively) [11, 13]. Whereas others have found either no relationship [7] or an inverse relationship [12] between the number of vessels involved and survival, we found a positive correlation. Likewise, survival positively correlated with the occurrence of diffuse atherosclerotic coronary disease, in contrast to the inverse correlation noted by Johnson and associates [15].

The number of grafts received is similar to that of other studies [11, 13]. In contrast to the findings of others [6], however, patients receiving a greater number of grafts fared worse, though this was not significant. The mean number of grafts was 1.9 for those who have died compared with 1.6 for those alive, despite the fact that survivors had a significantly greater number of vessels involved, findings that suggest incomplete revascularization. Incomplete revascularization has been shown to affect long-term survival in one study [12] but not in others [7, 8].

The 5-year survival of 89.8% in our patient population compares favorably with that reported by others [5–7, 9, 14]. The 10-year survival of 68.4% in this study is similar to that noted by some [6, 7, 9, 13], although less than the 80% shown by others [5, 11, 12, 14]. Loop and associates [3] reported 10-year survival rates of 88.0% for patients with one-vessel disease and 79.5% for those with two-vessel disease, which far exceed our 33% 10-year survival for each of these categories. However, our 69.2% 10-year survival for three-vessel disease compares well with the 71.0% in that study [3]. Our 53.1% 15-year survival likewise compares well with that reported previously [16]. We report a 20-year survival of 41% for saphenous vein CABG.

Cron and colleagues [11] stated that relatively few cardiac-related deaths occurred among CABG patients and that as many, if not more, died of cancer. Our study agrees with that of Coll Mazzei and co-workers [13] in that approximately 60% of all late deaths after primary operation will be cardiac in nature. In addition, up to 80% of late deaths after repeat operation will be due to cardiac-related causes.

We report a cumulative reoperative rate of 5%, 14%, 27%, and 36% at 5, 10, 15, and 20 years, respectively. This is similar to the 6% and 17% at 5 and 10 years, respectively, noted by Rahimtoola and associates [14]. Ten-year survival rates were nearly identical to those described by Lytle and colleagues [8].

Variations in the results of this study compared with those of others of the same era are likely due to the smaller number of patients in the current investigation. A word of caution is required. Although this study gives historical insight into the success of CABG 20 years ago, it cannot be used to predict the results of the operation today. In addition to technological advances, patient selection criteria have changed. The mean age has increased. The proportion of single-vessel and double-vessel disease has decreased. We continue to operate on progressively older patients with long-standing disease.

In conclusion, saphenous vein CABG in our earliest group of patients yielded a 41% 20-year survival. Cardiac-related causes continued to account for the majority of late deaths. Thirty-six percent of all patients and 53% of all long-term survivors underwent repeat operation. Repeat operation significantly influenced long-term survival.

We thank Jackie Dorsey for her continued tremendous energy in assisting with data collection, patient follow-up, and preparation of the manuscript.

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The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment. Overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to the replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis.

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Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards® pericardial valves must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards® pericardial valve could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in the sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C and 25°C (50-77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

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Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days), necessitating reoperation and replacement of the prosthetic device.

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Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards® pericardial bioprostheses to calcification as compared to commercially available bioprostheses.

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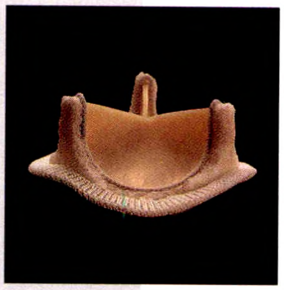

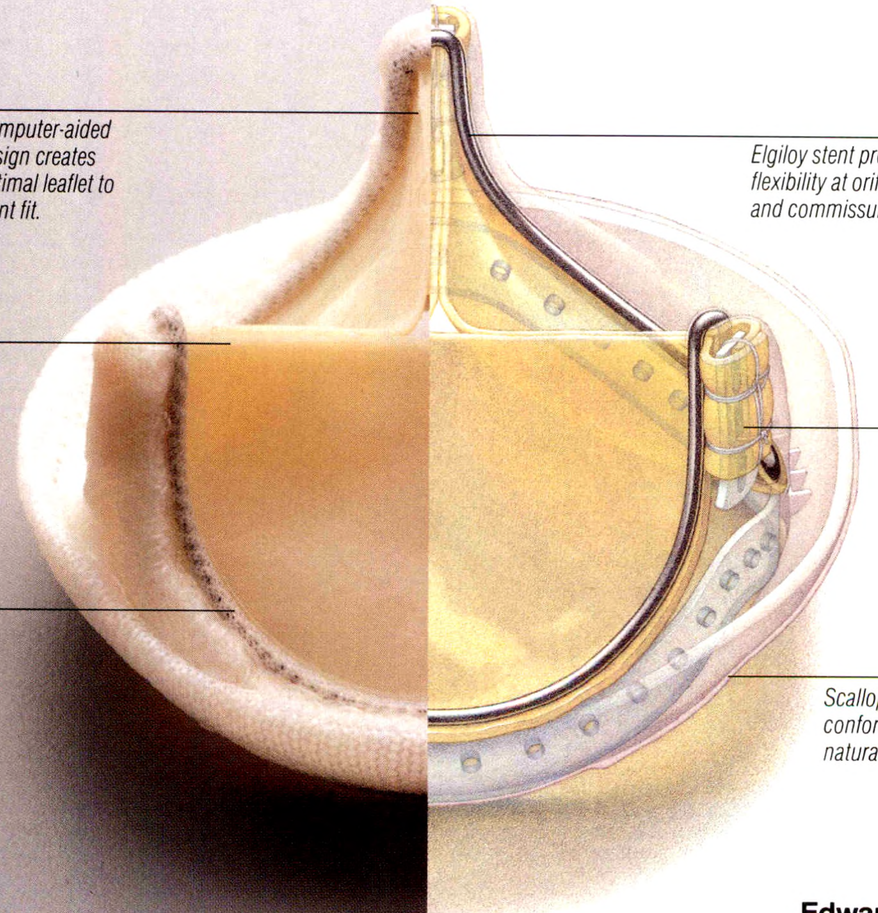
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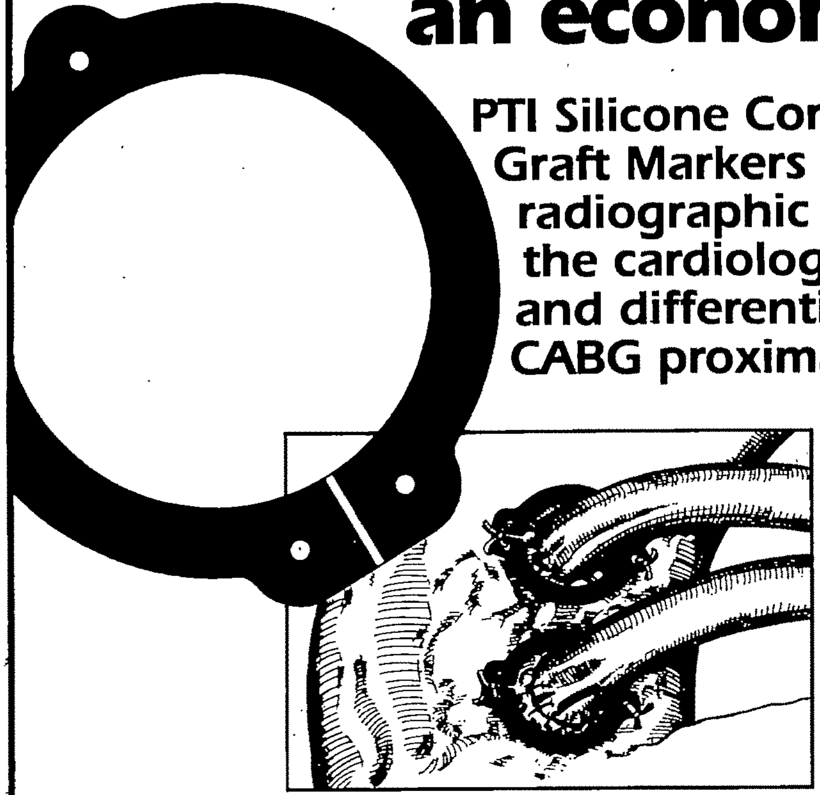

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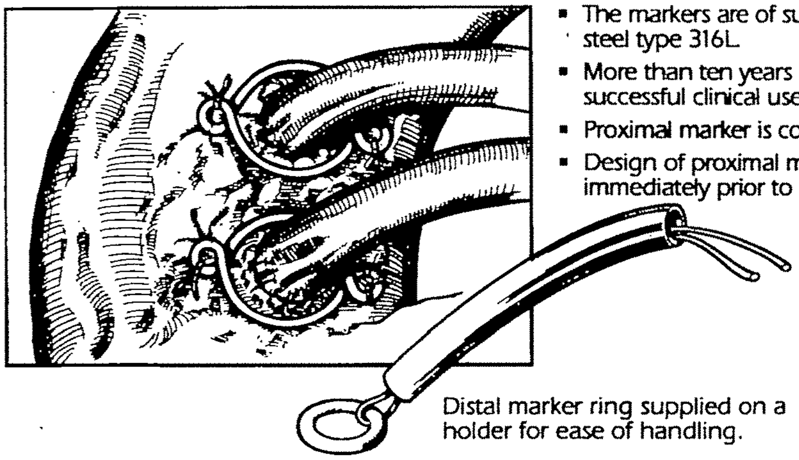

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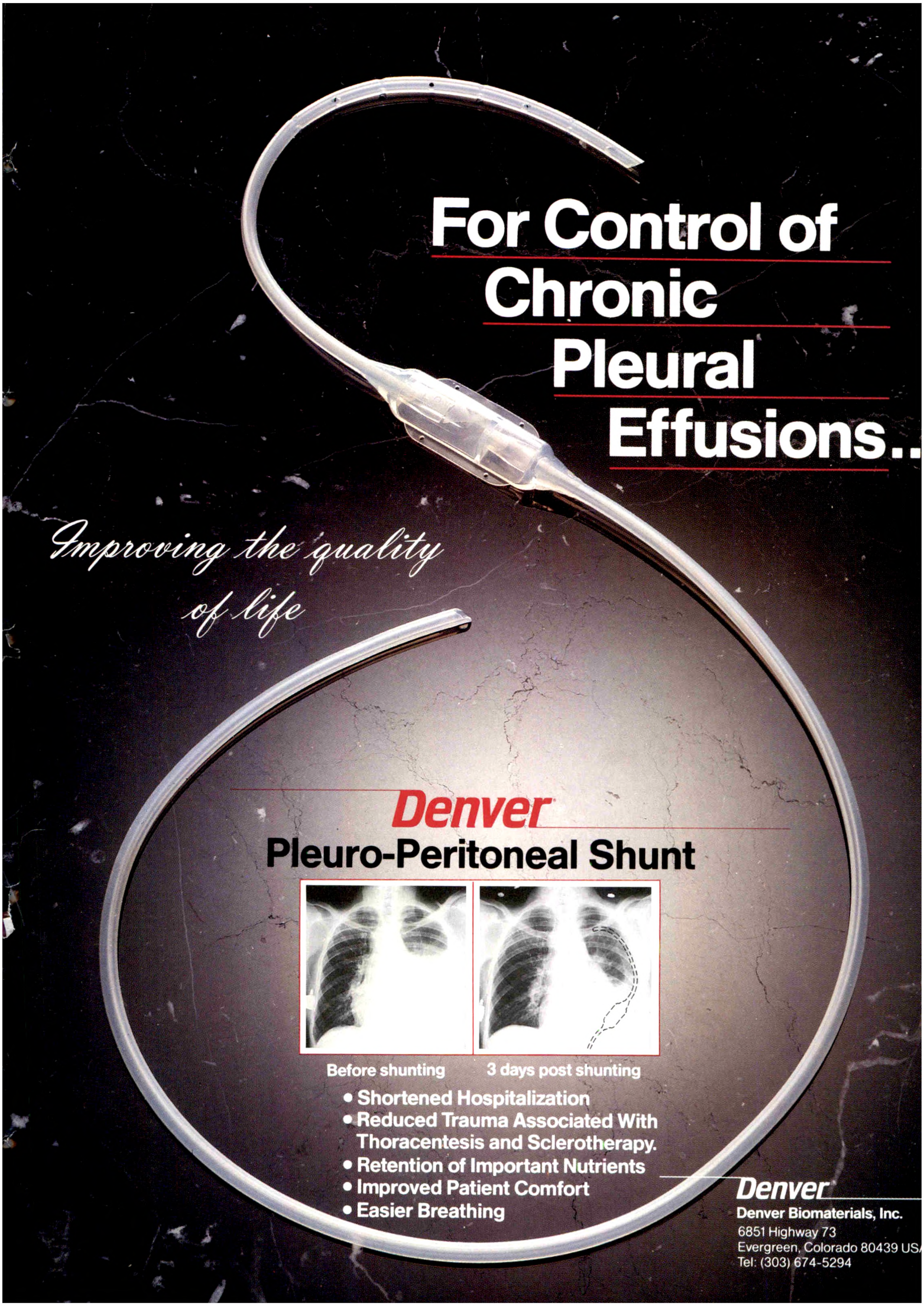

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Reoperation for Prosthetic Valve Endocarditis in the Third Trimester of Pregnancy

Stephen Westaby, FRCS, Andrew J. Parry, FRCS, and J. Colin Forfar, FRCP

Oxford Heart Centre, Oxford, England

A pregnant 29-year-old woman underwent emergency aortic valve re-replacement for prosthetic valve endocarditis. Cesarean section was performed with the chest open ready for cannulation. Fears of uterine hemorrhage during systemic heparinization for cardiopulmonary bypass were unfounded, and both mother and the 28-week-gestation newborn recovered uneventfully.

(Ann Thorac Surg 1992;53:263–5)

Surgical intervention for prosthetic valve endocarditis during pregnancy is complicated by the risks of cardiopulmonary bypass to the fetus as well as the technical problems of increased vascularity, bleeding tendencies, and the difficulties of reoperation through pericardial adhesions. Further, for prosthetic aortic valve replacement, sepsis or aneurysm formation in the annulus may necessitate prolonged manipulation to acquire secure valve implantation. A protracted operation is more likely to result in premature labor or fetal death even when full precautions are taken, including elevation of the right flank to displace the uterus from the inferior vena cava.

Nowadays a fetus of 28 weeks' gestation has a good chance of survival. Open cardiac operation in the third trimester might therefore be best managed by cesarean section followed immediately by cardiac operation using conventional techniques without time constraint. The outstanding consideration is whether cardiopulmonary bypass can be carried out safely without uncontrollable bleeding from the uterine bed. We present a case report that illustrates our approach to the problem and review the literature relevant to cardiopulmonary bypass during pregnancy.

Case Report

A 26-year-old woman who had previously had three successful pregnancies despite critical aortic stenosis was referred for aortic valve replacement. A heavily calcified bicuspid valve was excised and replaced with a 23-mm Carpentier-Edwards porcine xenograft. The biological valve was used because she was to remarry and, despite advice to the contrary, wanted more children. Anticoagulants were therefore contraindicated. She was not an intravenous drug abuser.

Three years later and 24 weeks into her fourth pregnancy, the patient had malaise, fatigue, night sweats, and hematuria after dental treatment without antibiotic prophylaxis. Her condition worsened despite antibiotic treatment, and at 26 weeks she was admitted to the hospital. A new soft ejection systolic murmur was detected, and splinter hemorrhages were seen in the toes of the left foot. Blood cultures grew *Streptococcus sanguis* sensitive to gentamicin sulfate and benzylpenicillin, and these were prescribed directly. Two-dimensional echocardiography showed prolific vegetations, particularly on the ventricular side of the aortic prosthesis. One of them prolapsed into the valve ring during systole and partially obstructed its orifice. An outflow gradient of 140 mm Hg was recorded by Doppler echocardiography during systole, but there was no aortic regurgitation.

The management of this patient stimulated considerable debate among the cardiology, cardiac surgical, obstetric, and pediatric teams. The risks to be considered were coronary or cerebral embolism from the infected prosthesis versus loss of the child during a potentially difficult valve re-replacement or after cesarean section at 26 weeks. Fetal survival was considered secure if delivery could be postponed until 28 weeks, and accordingly, medical management with antibiotics and close observation by serial electrocardiograms and echocardiograms was undertaken for a further 2 weeks.

At 28 weeks the patient was taken to the operating theater for cesarean section, which was to be followed directly by aortic valve replacement. The patient was anesthetized and positioned supine on the operating table but with the right flank elevated to displace the uterus from the inferior vena cava. As rapid sternotomy through previous adhesions would prove difficult in the event of acute deterioration, the mediastinal reentry was undertaken first. The pericardial adhesions over the anterior surface of the heart were cleared so that pursestrings could be inserted into the aorta and right atrium in preparation for bypass.

At this stage, a routine and uneventful lower-segment cesarean section was performed, delivering a live male infant weighing 1.3 kg. The uterus was closed in two layers, with great care taken to achieve full hemostasis. Sterilization was carried out by tubal ligation, and ergonovine (ergometrine) was administered systemically. The abdominal wound was left open in case of hemorrhage during full heparinization and cardiopulmonary bypass with muscle relaxants.

Cardiopulmonary bypass was established with systemic cooling to 32°C. As soon as perfusion was started,

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Table 1. Summary of Reported Cardiac Operations Performed With Cardiopulmonary Bypass During Pregnancy, 1959–1990

Procedure	No. of Patients	Indication for Operation	Maternal Deaths	Fetal Deaths
Open mitral commissurotomy	33	CHF, 27[a]	0	2
Mitral valve replacement	29	CHF, 21; endocarditis, 1; thrombosed prosthesis, 7	1	6
Aortic valve replacement	15	Aortic stenosis, 9; endocarditis, 6	0	5
Pulmonary embolectomy	4	Shock, 4	0	1
Closure of ASD or VSD	22	CHF, 8[a]	1	6
Coronary bypass	4	Unstable angina, 4	0	0
Myxoma removal	4	. . .		
Repair of thoracic aorta	3	Leaking/ruptured aneurysm, 3	0	0
Tetralogy of Fallot	1	. . .	0	0
Total	115		2 (1.7%)	20 (17.4%)

[a] Data in literature were incomplete.

ASD = atrial septal defect; CHF = congestive heart failure; VSD = ventricular septal defect.

the aortic cross-clamp was applied so that further manipulation would not disseminate fragile vegetations. The aortic root was opened and 1 L of cold potassium cardioplegia delivered directly into the coronary ostia. Inspection of the valve prosthesis showed it to be grossly infected, and on its removal from the annulus, the left ventricular outflow tract was found to be packed with vegetations. There was a subannular aortic root abscess between the left and right coronary cusps. All infected material was removed, and the valve was replaced with a size 11A Starr-Edwards prosthesis.

After systemic rewarming and reperfusion, the heart reverted to sinus rhythm spontaneously, and cardiopulmonary bypass was discontinued without difficulty. Thoracic and abdominal wounds were closed directly after heparin sodium reversal. The mother was transferred to the cardiac recovery area and extubated 1 hour later. She completed a course of antibiotics in the hospital over the next 4 weeks. The infant was transferred to the special-care baby unit and made satisfactory progress.

One year later, both mother and infant are in good health.

Comment

Table 1 summarizes the reported experience of open cardiac operations in pregnant patients. There have been many reports of fetal survival to term after cardiopulmonary bypass in the second and third trimesters of pregnancy [1]. It is generally accepted that closed mitral valvotomy and open heart procedures using cardiopulmonary bypass can be performed with very low risk to the mother. Collective reported experience [2–7] of more than 500 closed mitral valvotomies as early as 1965 showed a maternal mortality rate of less than 2% and a fetal mortality rate of less than 10%. Maternal mortality does not differ from that expected in the overall population according to the type of surgical procedure performed, and hence pregnancy should not influence the outcome in female patients requiring cardiac procedures. The review by Becker [8] of the experience of members of The Society of Thoracic Surgeons revealed only 1 maternal death in 68 operations with cardiopulmonary bypass, and that death occurred late and was due to hepatitis.

There have been no comprehensive experimental studies of the effects of cardiopulmonary bypass on the fetus. Theoretically, nonpulsatile perfusion, hyperoxygenation, heparinization, and prolonged hypotension could adversely affect both placenta and fetus. Fetal heart monitoring has shown dysrhythmias and bradycardia during perfusion [9]. Bradycardia occurs at the onset of bypass, a finding suggesting it is possibly related to hypothermia [9], and can be eliminated by an increase in perfusion rate. Thus high flow rates together with normothermic perfusion have reduced fetal risk during bypass. Intraoperative uterine monitoring shows the rewarming phase of bypass may promote uterine contractions and premature labor, particularly in mothers with advanced gestational age (between 26 and 35 weeks of pregnancy). These can be controlled by pharmacological inhibition, and this has been used successfully in 1 patient who went into labor during bypass [10].

Although case reports and collective reviews suggest that fetal mortality has become progressively less likely during cardiopulmonary bypass, prolonged valve operations still carry considerable risk. We have had experience with an intrauterine death during aortic valve replacement in a patient in the third trimester, despite the use of normothermic pulsatile perfusion with high flow rates in an attempt to preserve the fetus. Subsequent spontaneous abortion with profound hemorrhage also endangered the life of the mother. This adverse outcome was not reported, and the predominance of successful cases in the literature may reflect a general tendency not to report unsuccessful efforts.

When urgent open cardiac operation is required during the first or second trimester, there is little option other than to try to preserve the fetus. We have found no relationship between gestational age and mortality in reported cases, but congenital malformations were found at delivery in 3 infants whose mothers had undergone cardiopulmonary bypass during the first trimester. The optimum time for elective cardiac operation, however, is certainly outside of pregnancy, and we now consider it safer to deliver a fetus at 28 weeks or more rather than to risk bypass. Unlike 10 years ago, today neonatal pediatric intensive care is highly sophisticated, and the majority of these infants can be expected to survive.

Our literature search showed the fetal death rate was 17.4% for cases involving cardiopulmonary bypass (see Table 1). There were 6 fetal deaths among 29 patients who underwent mitral valve replacement during pregnancy. Of particular interest was thrombosis of mechanical mitral prostheses, which may follow a change in anticoagulant therapy from warfarin sodium to heparin sodium. Of 7 patients with valve thrombosis, 4 continued pregnancies to term after replacement, though 1 surviving infant had mild hydrocephalus. One fetus spontaneously aborted 3 days after operation, and 2 patients with a pregnancy of more than 35 weeks required urgent cesarean section, secondary to hemodynamic deterioration in the mother with fetal distress. The delivery was carried out before valve replacement in 1 patient and intraoperatively in the second; both infants survived. In another patient operated on for complications of mitral valve endocarditis, spontaneous abortion with fetal death occurred during the first postoperative day.

Aortic valve replacement also carries a major risk for the fetus. Of 9 patients requiring elective valve replacement for critical aortic stenosis, only 5 continued their pregnancy to term. As with our unpublished case, spontaneous abortion occurred within 3 days of operation in the other 4. Six patients underwent valve replacement for complications of native aortic valve endocarditis. One patient, whose term was unspecified but who was late in the third trimester, underwent cesarean section before valve replacement, and both mother and infant survived. There was 1 fetal death in the remaining 5 patients.

Infective endocarditis in itself does not appear to adversely affect the fetus. We know of 1 other patient who underwent cesarean section at 36 weeks' gestation before cardiopulmonary bypass for endocarditis (personal communication). The mother was in cardiogenic shock with a thrombosed and infected mitral disc valve, but both mother and infant survived.

The principle concern in the case of our patient was the potential for uterine hemorrhage during cardiopulmonary bypass after the cesarean section had been performed. There is little recorded experience with cesarean section in the peribypass state. Martin and associates [11] performed cesarean section for fetal distress during cardiopulmonary bypass with survival of both mother and child. We had intended to pursue this course in our patient whose fetus died but were misled by the intraoperative fetal monitoring.

Our experience, reinforced by these additional cases, leads us to conclude that for pregnancies of 28 weeks or more, cesarean section can be undertaken safely before bypass without risk of subsequent uterine hemorrhage. This seems preferable to attempting to preserve the fetus during bypass in the face of a reported fetal mortality rate of 17.4%, and we believe this option should be taken in preference to exposing the fetus to the risks of cardiopulmonary bypass.

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Availability of the In Situ Right Gastroepiploic Artery for Coronary Artery Bypass

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The right gastroepiploic artery (GEA) has been successfully used as a coronary bypass graft recently. We examined the in situ GEA graft length required from the pyloric portion to the site of coronary anastomosis at the time of operation. Measured GEA length was 17.0 ± 1.7 cm for the posterior descending artery anastomosis in 17 patients, 17.8 ± 1.7 cm for the main right coronary artery anastomosis in 13 patients, 22.0 ± 2.3 cm for the posterolateral branch anastomosis in 7 patients, and 21.0 cm for the left anterior descending artery anastomosis in 1 patient. We examined 228 randomly selected abdominal angiograms and measured the internal diameter of the right GEA at every 2-cm interval from its origin. Probability of availability of the in situ GEA graft for each site of anastomosis was 97% to the right coronary artery and 88% to the anterior descending or the circumflex artery when the internal diameter of GEA was 1.5 mm or greater. From an anatomical standpoint, we concluded that the GEA can be assumed available without preoperative angiography.

(Ann Thorac Surg 1992;53:266–8)

The right gastroepiploic artery (GEA) was introduced for direct coronary artery revascularization in 1974 by Dr W. Sterling Edwards [1] and was revisited successfully as a suitable arterial conduit for coronary artery bypass in 1987 [2, 3]. Patency of the GEA graft is favorable in the short-term period [1, 4, 5]. To know the availability of GEA grafts in terms of length and diameter, we examined the GEA profile at the time of operation and angiography.

Material and Methods

Of 41 patients undergoing coronary artery bypass grafting using GEA at Mitsui Memorial Hospital in 1990, the GEA graft was anastomosed to the main right coronary artery in 13 patients, to the posterior descending artery in 17 patients, to the posterolateral branch of the circumflex artery in 10 patients (Fig 1), and to the left anterior descending artery in 1 patient. The GEA graft length between the pylorus and the site of anastomosis was measured intraoperatively. The pedicled GEA graft was raised up to the pericardial cavity through the diaphragm, passing in front of the stomach and the liver in all patients as described previously [3, 4].

Two hundred twenty-eight abdominal angiograms performed at the Mitsui Memorial Hospital were examined to measure the length and diameter of GEA (patient age range, 33 to 80 years; mean age, 61.4 years; male/female ratio, 197:31). The profile of these patients was as follows: primary liver tumor, 179 patients; metastatic liver tumor, 10 patients; choleductal tumor, 7 patients; and other intraabdominal disorders, 32 patients. Opacification was achieved by injecting 50 mL of aqueous 38% iodide solution through an automatic syringe at a rate of 33 mL/s. To study the topography of GEA, the internal diameter and distance from the subpyloric gastroepiploic arterial orifice were measured. Obtained length was corrected for the magnification produced by roentgenography by a factor of 0.87. Internal diameter of GEA was measured at each 2-cm interval from its origin to the portion where its internal diameter decreased to less than 0.5 mm. The length was explained by mean ± standard deviation. By the histographic method, probability curves were drawn to describe the availability of the in situ GEA for coronary artery bypass grafting (Fig 2).

Results

The mean intraoperative length from the pylorus to the anastomosis was 17.0 ± 1.7 cm (range, 14 to 20 cm) for the posterior descending artery, 17.8 ± 1.7 cm (range, 16 to 22 cm) for the main right coronary artery, 22.0 ± 2.3 cm (range, 19 to 26 cm) for the posterolateral branch, and 21.0 cm for the left anterior descending artery. The mean body surface area of these patients was 1.65 ± 0.12 m^2 (range, 1.25 to 2.03 m^2). Postoperative angiography performed at 10 days to 2 months (average, 17 days) showed 34 of 35 GEA grafts were patent (one graft to the posterior descending artery was occluded).

Distal internal diameter of the GEA grafts just proximal to the anastomosis ranged from 1.9 to 2.5 mm with a mean of 2.1 mm. In the 228 abdominal angiograms examined, GEA arose from the gastroduodenal artery in 208 patients (91.2%) and from the superior mesenteric artery in 19 patients (8.3%). In 202 patients in whom the entire route of the GEA could be examined clearly, the mean internal diameter just proximal to the gastroduode-

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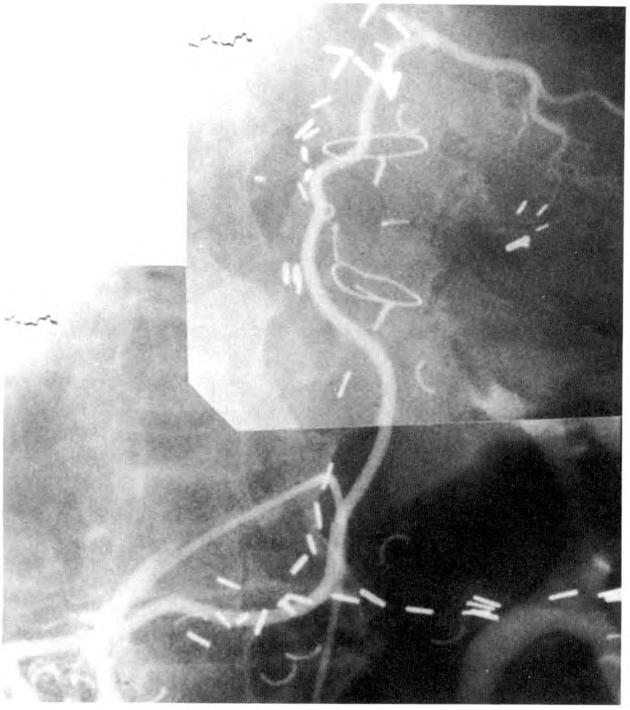

Fig 1. *Angiogram of the right gastroepiploic arterial graft with a length of 22 cm and a distal internal diameter of 2.5 mm anastomosed to the circumflex artery.*

nal artery was 3.47 ± 0.78 mm (range, 2.0 to 6.0 mm). The mean GEA length with an internal diameter of 3.0 mm was 11.3 ± 9.3 cm (range, 0 to 40 cm), that with a diameter of 2.5 mm was 18.5 ± 9.2 cm (range, 0 to 42 cm), that with a diameter of 2.0 mm was 25.0 ± 7.5 cm (range, 0 to 45 cm), and that with a diameter of 1.5 mm was 29.5 ± 6.1 cm (range, 8 to 45 cm) from the origin. Measurement of the internal diameter at every 2-cm interval from the origin of the right GEA to the portion where the internal diameter decreased to less than 0.5 mm is shown in a histographical curve in Figure 2. For example, at the portion 20 cm distant from the origin of the GEA, 192 of 202 cases (95.0%) have an internal diameter greater than 1.5 mm, 152 of 202 cases (75.2%) have an internal diameter greater than 2.0 mm, and 95 of 202 cases (47.0%) have an internal diameter greater than 2.5 mm.

Comment

Arterial grafts have been widely accepted for coronary artery bypass grafting because of the good long-term patency found in use of the internal thoracic artery [6], although the radial artery did not show good long-term patency [7]. There are few data regarding availability of the in situ GEA graft, although there are some reports on the internal thoracic artery in coronary artery bypass grafting [8]. Angiographic anatomical study of the GEA has been performed in replacement of the esophagus with a vascularized gastric tube that is fed by GEA alone [9, 10]. We now know that there is no gastric ischemia caused by take-down of GEA and there is no increase of surgical risk with use of GEA in coronary artery bypass grafting [11]. The size, free flow, and short-term patency of GEA grafts were similar to those of the internal thoracic artery [12].

Inspecting the abdominal angiograms with our histogram (see Fig 2), 97% of the in situ GEAs were available to bypass the posterior descending artery or the right coronary artery and 88% were available for the circumflex branches or the left anterior descending artery with an anastomotic diameter more than 1.5 mm by the anterior route. As we stated, we always put the GEA pedicle in front of the liver and the stomach even if the target is the posterior descending or the circumflex artery because it is technically easier and because it is easy to check for bleeding from the pedicle after completion of the anastomosis. The posterior route, with the graft located behind the liver and the stomach, might be accessible with shorter graft length to the posterior heart. However, we still do not attempt the posterior route because of the reasons mentioned, and to date we have found no difficulty in length of the graft with the anterior route. The body size of Japanese patients is apparently smaller than that of North American people, as we previously described [13]. The correlation of size between GEA and body surface area is unknown, however. Americans and Europeans with larger body structure may have larger GEAs.

From this study, we conclude that the in situ GEA graft is generally available in coronary artery bypass grafting.

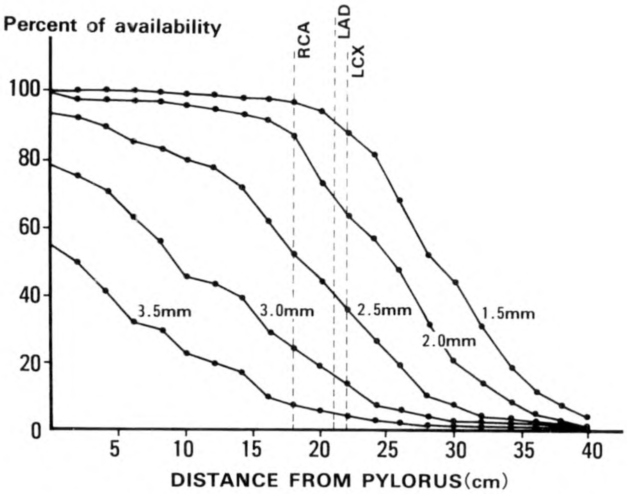

Fig 2. *Histogram of anastomotic diameter and graft availability of the in situ right gastroepiploic artery (n = 202). From the abdominal angiograms, the internal diameter of the gastroepiploic artery was measured at every 2-cm interval from its orifice to its end. The probability curves show each 0.5 mm of internal diameter from 1.5 to 3.5 mm with a magnification correction factor of 0.87.* The dotted lines *in the figure show mean required distances from the pylorus to each of the anastomotic sites measured intraoperatively. In this figure, for example, to anastomose in situ gastroepiploic artery with an internal diameter greater than 2.0 mm to the posterior descending artery, availability of gastroepiploic artery is 89.3%.* (LAD = *left anterior descending artery;* LCX = *circumflex artery;* RCA = *right coronary artery.)*

From an anatomical standpoint, preoperative celiac angiography may not be necessary as a routine procedure.

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Changing Profiles of Failed Coronary Angioplasty Patients: Impact on Surgical Results

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As more high-risk patients undergo percutaneous transluminal coronary angioplasty (PTCA), the changing profiles of PTCA patients who may require emergent coronary artery bypass grafting may alter operative morbidity and mortality. This study compared profiles of recent patients undergoing emergent coronary artery bypass grafting after a failed PTCA with earlier patients to determine their impact on operative results. From 1980 to 1988, 53 patients underwent emergent coronary artery bypass grafting after a failed PTCA at the Boston University Medical Center. These patients were divided into two groups based on the year of the PTCA: group I, 1980 to 1985 (n = 18); and group II, 1986 to 1988 (n = 35). Group II patients tended to be older (age ≥65 years, 47% group II versus 11% group I), were more likely to have unstable angina before PTCA (74% versus 33%), and had lower ejection fractions (0.53 ± 0.02 versus 0.63 ± 0.05) and more vessels with 50% or greater stenosis (2.1 ± 0.2 versus 1.6 ± 0.2). Nevertheless, there was no significant difference in the incidence of perioperative myocardial infarcts using enzyme and electrocardiographic criteria (37% in group II versus 39% in group I), 30-day operative mortality (11% in group II versus 11% in group I), or major postoperative complications (14% in group II versus 22% in group I). We conclude that despite the changing profiles of patients undergoing PTCA, which include older patients with more extensive coronary artery disease and lower ejection fractions, operative results after emergent coronary artery bypass grafting for failed PTCAs remain unchanged.

(Ann Thorac Surg 1992;53:269–73)

Percutaneous transluminal coronary angioplasty (PTCA) is now an accepted method of revascularization for patients with single-vessel and multivessel disease. In 1979, the National Heart, Lung, and Blood Institute established a registry for PTCA patients to evaluate the safety and efficacy of this technique [1]. In 1985, the registry was reopened to document changes in angioplasty strategies and outcomes [2]. This study compared patients undergoing PTCA in the period 1985 to 1986 with the earlier registry patients from 1977 to 1981. Patients undergoing PTCA in 1985 to 1986 were older with a higher incidence of unstable angina and had a significantly higher proportion of multivessel disease, poorer left ventricular function, and a higher incidence of previous myocardial infarctions (MIs). These patients also had more complex coronary lesions and more multilesion angioplasties.

As more of these high-risk patients undergo PTCA, the changing profiles of angioplasty patients who might require emergent coronary artery bypass grafting (CABG) after a failed PTCA may alter operative morbidity and mortality. This study was therefore undertaken to compare the profiles of our recent emergent CABG patients (1986 to 1988) after a failed angioplasty with earlier patients (1980 to 1985) to determine their impact on surgical results.

Material and Methods

During the period from March 1, 1980, through December 31, 1988, 2,900 PTCAs were performed at the Boston University Medical Center (Fig 1). In 53 (1.8%) of these patients, emergent CABG was required because of acute myocardial ischemia during or immediately after the PTCA. These patients were divided into two groups based on the year of their PTCA (see Fig 1). Group I was composed of 18 patients who required emergent CABG after a failed PTCA in the years 1980 to 1985. Group II consisted of 35 patients requiring an emergent CABG in the years 1986 to 1988.

During the period of this study, standard protocols were established for surgical support of all PTCA procedures. All patients were prepared for operation the night before their PTCA and were visited by a member of the surgical team. From 1980 to 1986, an operating room was specifically made available during all PTCA procedures for possible surgical intervention. In 1987, this policy was changed such that all CABG procedures following an

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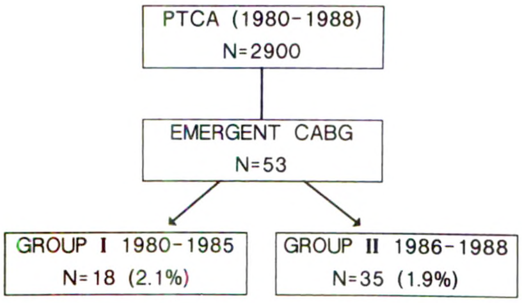

Fig 1. Algorithm for the two groups studied. (CABG = *coronary artery bypass grafting;* PTCA = *percutaneous transluminal coronary angioplasty.)*

unsuccessful PTCA would be performed in the next available operating room. Because all operating rooms were capable of supporting cardiopulmonary bypass equipment, all rooms in the operating suite could be used even when the designated "heart rooms" were being used.

Standard percutaneous angioplasty techniques were used [3]. A coronary occlusion during PTCA was defined as a vessel that became occluded during angioplasty and remained occluded at the end of cardiac catheterization. If the PTCA was unsuccessful but the patient had no evidence of acute myocardial ischemia, CABG was performed on an elective date. These patients were not included in this study. Refractory myocardial ischemia with an inadequate angioplasty outcome resulted in emergent CABG. Patients with hemodynamic instability and ongoing ischemia despite maximal medical management received an intraaortic balloon pump. In 1987, reperfusion catheters became available in our institution to establish temporary reperfusion to areas of the myocardium distal to the occlusion [4]. These were inserted whenever technically possible and removed during the operation just before aortic clamping. Percutaneous bypass was not available at our institution during this study period.

Patients were rapidly transported to the operating room, cannulated, and placed on cardiopulmonary bypass. The decision to use an internal mammary artery graft was based on the coronary anatomy, segmental wall motion of the region being grafted, and the hemodynamic stability of the patient. Myocardial protection was achieved with antegrade, potassium, crystalloid and blood cardioplegic solutions supplemented with systemic (28°C) and topical hypothermia. All vessels with at least a 50% lesion were bypassed. All distal anastomoses were performed during one period of ischemic arrest with the anastomoses to the vessel involved during the PTCA performed first. Cardioplegic solution was given down each vein graft after the completion of each distal anastomosis. The time to revascularization was defined as that period from the start of coronary occlusion in the catheterization laboratory to the restoration of blood flow through a completed bypass graft in the operating room. A perioperative MI was diagnosed either by the appearance of new permanent electrocardiographic (ECG) changes using the Minnesota Code or by the elevation of the myocardial fraction of creatine kinase to greater than 50 IU in the immediate 24-hour period after operation as previously described [5].

Statistical analysis was performed in consultation with the Department of Biostatistics at the Boston University Medical Center. Differences in proportion between patient subgroups were assessed by χ^2 testing. Differences in patient variables measured in a continuous scale were assessed by nonpaired Student's *t* test. Nonnormalized data were analyzed using Wilcoxon nonparametric tests. Confidence intervals were calculated when appropriate. All meaned data represent the mean ± standard error, and differences were considered significant when *p* values were less than 0.05.

Results

The results are summarized in Tables 1 through 4. During the period of 1980 to 1985 (group I), 2.1% of all patients undergoing PTCA required an emergent CABG. The rate of emergent CABG during 1986 to 1988 (group II) was 1.9%, which was not significantly different from that of group I (see Fig 1).

The patient profiles of the two groups are listed in Table 1. Although there was no significant difference in mean age between the groups (58 ± 2 years in group I versus 61 ± 2 years in group II; not significant [NS]), group II had a significantly higher percentage of patients 65 years old or older (46% versus 11%; $p < 0.03$). Group II patients also tended to have more symptomatic coronary disease as seen by a significantly higher percentage of patients with unstable angina (74% versus 33%; $p < 0.004$). The incidence of risk factors such as hypertension, congestive heart failure, and diabetes was similar in both groups. Group II patients, however, did have significantly lower ejection fractions on their preoperative ventriculograms (0.52 ± 0.02 versus 0.63 ± 0.05; $p < 0.05$).

The PTCA and catheterization profiles are listed in Table 2. Group II patients had a significantly greater number of vessels with 50% or greater stenosis (2.1 ± 0.2

Table 1. Patient Profiles

Variable	Group I: 1980–1985 (n = 18)	Group II: 1986–1988 (n = 35)	*p* Value
Mean age (y)[a]	58 ± 2	61 ± 2	NS
Age ≥65 y	2 (11%)	16 (46%)	<0.03
Males/females	12/6	23/12	NS
Unstable angina	6 (33%)	26 (74%)	<0.004
Hypertension	5 (28%)	14 (40%)	NS
Congestive heart failure	0 (0%)	0 (0%)	NS
Diabetes	2 (11%)	5 (14%)	NS
Ejection fraction[a,b]	0.63 ± 0.05	0.53 ± 0.02	<0.05

[a] Data represented as mean ± the standard error. [b] Ejection fraction was based on preoperative ventriculograms.

NS = not significant

Table 2. Percutaneous Transluminal Coronary Angioplasty and Catheterization Profiles

Variable	Group I: 1980–1985 (n = 18)	Group II: 1986–1988 (n = 35)	p Value
Vessels with ≥50% stenosis[a]	1.6 ± 0.2	2.1 ± 0.2	<0.05
Multivessel PTCA	3 (17%)	5 (14%)	NS
Closure Type			
Occlusion	4 (22%)	18 (54%)	<0.05
Dissection	4 (22%)	11 (31%)	NS
Occlusion & dissection	10 (55%)	6 (17%)	<0.05
Insertion of reperfusion catheter	0 (0%)	7 (20%)	<0.05
Preop IABP	16 (80%)	27 (70%)	NS
Inotropic support after PTCA	2 (11%)	8 (23%)	NS
ECG changes after PTCA	10 (56%)	17 (49%)	NS

[a] Data represented as mean ± the standard error.

ECG = electrocardiographic; IABP = intraaortic balloon pump; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

Table 4. Surgical Results

Variable	Group I: 1980–1985 (n = 18)	Group II: 1986–1988 (n = 35)	p Value	95% CI
30-day mortality	2 (11%)	4 (11%)	NS	−17.6–18.3
Cardiac related	1	3	NS	
Major complications	4 (22%)	5 (14%)	NS	−30.4–14.5
Hemorrhage	2	2	NS	
Respiratory insufficiency	1	0	NS	
Sternal infection	1	2	NS	
CVA	0	1	NS	
Myocardial infarction	12 (67%)	17 (49%)	NS	−45.5–9.3
Enzyme elevation	5 (28%)	4 (11%)	NS	
Enzyme elevation & ECG changes	7 (39%)	13 (37%)	NS	

CI = confidence interval; CVA = cerebrovascular accident; ECG = electrocardiographic; NS = not significant.

versus 1.6 ± 0.2; $p < 0.05$); however, the incidences of attempted multivessel PTCAs were similar in both groups. Failures of PTCA were more likely to result from coronary occlusion in group II patients (54% versus 22%; $p < 0.05$), whereas group I patients were more likely to have a combination of occlusion and dissections (55% versus 17%; $p < 0.05$). None of the patients in group I had the insertion of a reperfusion catheter, whereas this device was used in 7 patients (20%; $p < 0.05$) in group II. The incidence of insertion of a preoperative intraaortic balloon pump (80% in group I versus 70% in group II; NS) and the need for preoperative inotropic support (11% in group I versus 23% in group II; NS) were similar in both groups. The presence of ECG changes after the PTCA before emergent CABG was not significantly different between group I and group II patients (56% in group I versus 49% in group II; NS).

Table 3 reviews the intraoperative data. The mean number of vessels bypassed and the incidence of multivessel CABG were similar in both groups. Cross-clamp time was not significantly different between group I and group II patients (33.8 ± 3.7 minutes in group I versus 36.4 ± 3.2 minutes in group II; NS). The time to revascularization was, however, more prolonged for patients in group II (144 ± 5 versus 168 ± 8 minutes; $p < 0.02$). The internal mammary artery graft was more frequently used in group II patients (40% versus 6%; $p < 0.008$).

The surgical outcomes are listed in Table 4. Thirty-day operative mortality was identical in both groups (11% versus 11%; NS). There were two deaths in the group I patients. One patient had development of cardiogenic shock in the catheterization laboratory and died of a sudden episode of ventricular tachycardia on the first postoperative day. The other patient was a Child's class C cirrhotic who died of fulminant sepsis and hepatic failure. There were four deaths in the group II patients. All four patients had cardiac arrests in the catheterization laboratory and were brought to the operating room receiving large doses of inotropes, on an intraaortic balloon pump, and in cardiogenic shock. One of these patients could not be weaned from cardiopulmonary bypass, another died on the fourth postoperative day of low cardiac output syndrome, a third died of a massive cerebrovascular accident, and the fourth had a sudden episode of ventricular tachycardia on the seventh postoperative day.

The incidence of major complications was not significantly different between groups (22% in group I versus 14% in group II; NS). Of the four major postoperative

Table 3. Operative Data

Variable	Group I: 1980–1985 (n = 18)	Group II: 1986–1988 (n = 35)	p Value
Mean number of vessels bypassed[a]	1.7 ± 0.5	2.1 ± 0.1	NS
CABG × 1	9 (50%)	10 (28%)	NS
CABG × 2	4 (22%)	12 (33%)	NS
CABG × ≥3	5 (27%)	13 (37%)	NS
Cross-clamp time (min)[a]	33.8 ± 3.7	36.4 ± 3.2	NS
Time to revascularization (min)[a]	144 ± 5	168 ± 8	<0.02
LIMA	1 (6%)	14 (40%)	<0.008

[a] Data represented as mean ± the standard error.

CABG = coronary artery bypass grafting; LIMA = left internal mammary artery.

complications in group I patients, two involved reoperation for bleeding; 1 patient had a sternal infection and 1 patient required prolonged ventilatory support. The five postoperative complications in the group II patients included bleeding requiring reoperation in 2 patients, sternal infection in 2, and a cerebrovascular accident in 1. There was evidence of an MI in 67% of group I patients, of whom 28% had evidence of enzyme elevation and 39% had both enzyme and ECG changes. In the 49% of group II patients with evidence of MI, 37% had both enzyme elevation and ECG changes. The patterns and incidence of MI were not significantly different between the two groups. Of the 7 patients who had insertion of reperfusion catheters, 4 had evidence of ECG changes before the insertion of the catheter. Three of these patients subsequently went on to have a perioperative MI documented by ECG changes and enzyme elevations.

Comment

Recent and evolving changes in the practice of cardiology, emphasizing PTCA for multivessel disease and extending periods of medical therapy, have resulted in significant changes in the profiles of patients now undergoing CABG [6, 7]. Naunheim and associates [6] found that, when compared with 100 consecutive patients undergoing isolated CABG in 1975, a similar cohort of CABG patients in 1985 were significantly older and had more extensive coronary disease, poorer left ventricular function, and more associated medical illnesses. This resulted in an increased operative mortality, primarily in patients undergoing emergent operation. Similar findings were reported by Jones and associates [7] comparing the outcomes of CABG patients in 1981 and 1987. Because emergent myocardial surgical revascularization is the accepted therapy for patients with acute ischemia after an unsuccessful PTCA, this study sought to determine whether the changing profiles of patients coming to PTCA would alter surgical results after emergent CABG for a failed PTCA.

The changing profiles of our most recent failed PTCA patients (group II; 1986 to 1988) were similar to those seen in the recent national PTCA registry study [2]. A higher percentage of group II patients were older than 65 years, and group II patients had a significantly higher incidence of unstable angina. Their preoperative ejection fractions were lower and they had more extensive coronary disease. Despite the more complex and extensive coronary lesions, the incidence of unsuccessful PTCAs was only 1.9%, which reflects improvements in catheter designs, angioplasty techniques, and the skills of the interventional cardiologists.

The incidence of ECG changes after PTCA was unchanged in both groups. Along with others, we have previously shown that patients with ECG changes immediately after an unsuccessful PTCA have a higher incidence of perioperative MIs [5, 8]. In 1986, reperfusion catheters were introduced into clinical practice at Boston University, and they were used in 7 patients in group II. Ferguson and associates [9] found that these catheters helped to reverse the ECG changes seen after failed PTCA and reduced the incidence of perioperative MIs. Douglas and colleagues [10], however, failed to show any difference in the frequency of Q-wave MIs and peak levels of creatine kinase-MB in 40 matched patients using reperfusion catheters. Of the 7 patients in whom reperfusion catheters were used in this study, 4 had development of ECG changes after their PTCA. Three of these patients went on to have an MI as evidenced by ECG and enzyme changes. It is uncertain, however, whether the absence of a reperfusion catheter would have resulted in a larger area of necrosis.

Although the time to revascularization was significantly longer in the group II patients (168 ± 8 versus 144 ± 5 minutes; $p < 0.02$), the incidence of MIs was not significantly different. This is consistent with our previous findings and those of others [5, 11]. The longer time to revascularization in group II patients may reflect our change in operating room standby policy adopted in 1987, where emergent CABGs after a failed PTCA were triaged to the next available room. The fact that the mean difference between the two groups was only 24 minutes and that this delay resulted in no increase in mortality or infarct rate tends to support the "next available room" backup system provided that there is close communication between the catheterization laboratory and the operating room [12].

Despite the higher risk of group II patients, there was no significant increase in the incidence of 30-day operative mortality, major complications, or MIs. The use of the left internal mammary artery graft and initiation of a next available room backup system in our series had no effect on the operative outcome. Our clinical results are similar to several of the studies recently reviewed by Greene and co-authors [13]. Of the six deaths in this series, five occurred in patients who were in cardiogenic shock after their failed PTCA. These patients are at a particularly higher risk for perioperative death and ventricular arrhythmias.

We conclude from this study that acceptable surgical results can still be obtained after emergent CABG for failed PTCA despite the increased incidence of preoperative risk factors. We suspect that our results can be attributed to (1) prompt and early detection of coronary ischemia while the patient is still in the catheterization laboratory, (2) the continued use of devices that favorably alter the supply-demand balance (intraaortic balloon pump and reperfusion catheters), and (3) our practice of rapid deployment to the operating room when all reasonable methods to establish blood flow have failed. Although the debate continues as to whether PTCA or surgical intervention is the better method for treating coronary artery disease, our study continues to support the premise that patients who sustain ischemic complications after PTCA are best treated by expeditious surgical revascularization.

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Platelet-Leukocyte Plasmapheresis Attenuates the Deleterious Effects of Cardiopulmonary Bypass

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A method of harvesting a high yield of concentrated platelet- and leukocyte-rich plasma was developed with the goal of attenuating some of the deleterious effects of cardiopulmonary bypass. The study involved 32 patients who underwent coronary artery bypass grafting with plasmapheresis before cardiopulmonary bypass and a control group of 32 patients who did not have plasmapheresis. A volume of 857 ± 359 mL of platelet- and leukocyte-rich plasma was concentrated from 4.6 ± 1.5 L of blood, and red cells and plasma were returned to the patient. The platelet- and leukocyte-rich plasma contained yields of $3.5 \pm 1.4 \times 10^{11}$ platelets and $3.4 \pm 1.9 \times 10^{9}$ leukocytes. There were no differences in age, sex, duration of cardiopulmonary bypass, and major risk factors between groups. However, total mediastinal chest tube drainage was 788 ± 542 mL in the controls and 425 ± 207 mL in the plasmapheresis group ($p < 0.01$). Homologous units transfused were 3.9 ± 2 in controls and 1.6 ± 2 in the plasmapheresis group ($p < 0.01$). Arterial oxygen tension on extubation was 94 ± 32 mm Hg in controls and 119 ± 25 mm Hg in the plasmapheresis group ($p < 0.01$). This technique of platelet and leukocyte protection results in reduced postoperative bleeding, a decreased need for homologous blood products, and improved pulmonary function.

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Increasing periods of cardiopulmonary bypass result in platelet activation by blood contact with the extracorporeal circuit. These activated platelets aggregate and form microemboli in the pulmonary and systemic circulation, resulting in a progressive decline in the platelet count [1–9]. Associated with this platelet activation is a widespread systemic inflammatory response involving neutrophils and numerous circulating inflammatory mediators. The results of such processes are injurious effects on multiple organs [2]. The vast majority of patients convalesce normally with minor evidence of morbidity. Occasionally, however, prolonged morbidity will accompany even successful operations. This so-called postperfusion syndrome is most widely recognized by varying degrees of pulmonary dysfunction, coagulopathy, extravascular fluid retention, and renal and other organ dysfunction [2].

It seems reasonable that the clinical manifestations of capillary damage and subsequent organ dysfunction are quantitatively related to platelet and leukocyte sequestration in the microcirculation by a possible mass action effect. The withdrawal before cardiopulmonary bypass (CPB) of a substantial mass of leukocytes and platelets may reduce the amount of capillary microembolism, and hence organ damage.

The collection of platelet-rich plasma (PRP) with reinfusion after CPB has been shown to decrease postoperative bleeding [10] and reduce homologous transfusion requirements [11, 12]. Our method of platelet and leukocyte collection differed from those used by other workers [10–12]. We made an aggressive attempt to maximize the yield of platelets and leukocytes in a concentrated preparation of PRP and achieved yields of up to 30% of estimated circulating leukocytes and platelets by processing as much as 6,000 mL of the patient's blood volume.

Material and Methods

After obtaining institutional approval and with informed patient consent we introduced platelet-leukocyte plasmapheresis (PLP) in March 1991. The plasmapheresis group was composed of 32 consecutive patients who were seen for operation in March and April. A control group of 32 patients was randomly selected from patients who underwent operation by the same surgeons in January and February 1991. All aspects of care remained identical during this interval with the exception of the introduction of PLP.

Membrane oxygenators, blood cardioplegia, and topical ice slush saline solution in the pericardial space were used. Myocardial temperatures were 6° to 10°C. Patients were systemically cooled to 28°C and then rewarmed to 37°C before separation from cardiac bypass. Fiberoptic pulmonary artery catheter monitoring was used. Patients undergoing initial or redo coronary artery bypass grafting were included. The vast majority of patients were ventilated overnight and extubated the following morning. Blood gases after extubation were measured while the patient breathed an inspired oxygen fraction of 0.50 through a face mask.

Our PLP technique involved drawing blood from a central venous line to a 225-mL bowl of an intraoperative

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Table 1. Summary of Results[a]

Variable	Control Group	Plasmapheresis Group	p Value
No. of patients	32	32	
Age (y)	65 ± 12	64 ± 10	NS
Sex (% male)	72%	65%	NS
Repeat CABG	0	1	NS
Return for bleeding	2	0	NS
CPB time (min)	119 ± 33	112 ± 44	NS
Elective/emergency operation	85%	87%	NS
Unstable angina	4	5	NS
MI within 7 days	1	2	NS
Ejection fraction <0.4	4	6	NS
Diabetes	4	3	NS
PaO_2 (3 L/min nasal) preop (mm Hg)	127 ± 14	131 ± 18	NS
PaO_2 (mm Hg)/FIO_2 on arrival in ICU	214 ± 45	249 ± 69	0.02
Postextubation gas exchange			
PaO_2 (mm Hg)	94 ± 32	119 ± 25	<0.01
PaO_2 (mm Hg)/FIO_2	188 ± 64	238 ± 50	<0.01
SaO_2	0.95 ± 0.06	0.98 ± 0.009	<0.01
Total MCT drainage (mL)	788 ± 542	425 ± 207	<0.01
HBT (U)	3.9 ± 2	1.6 ± 2	<0.01
Homologous platelets (U)	0.7 ± 0.7	0	<0.01
Homologous FFP (U)	2.2 ± 3.4	0.1 ± 0.4	<0.01

[a] Where appropriate, values are shown as mean ± standard deviation.

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; FIO_2 = inspired oxygen fraction; FFP = fresh frozen plasma; HBT = homologous blood transfusions; ICU = intensive care unit; MCT = mediastinal chest tube; MI = myocardial infarction; NS = not significant; PaO_2 = arterial oxygen tension; SaO_2 = arterial oxygen saturation.

blood salvage machine (AT750; Electromedics, Englewood, CO) while adding citrate-phosphate-dextrose in a ratio of 7:1. Separation of blood into three components was continued until 225 mL of red blood cells were collected in the centrifuge bowl. The first portion of platelet-poor plasma (approximately 300 mL), produced at a centrifuge speed of 5,000 rpm, was subsequently pooled with the red blood cells and returned to the patient. The PRP was collected in a separate bag at a centrifuge speed of 2,400 rpm. This fraction, approximately 100 mL, contained the buffy coat and the first 50 mL of red blood cells to maximize the yield of platelets and leukocytes. Each PLP cycle took 10 to 12 minutes to complete. The cycles were repeated as often as possible in the time between placement of monitoring lines and the administration of heparin. Therefore the collected volumes and cellular yields varied considerably between patients.

The PRP was stored and occasionally agitated at room temperature until reinfusion after weaning from CPB and protamine administration. Plasma volume was replaced with Normosol as dictated by hemodynamic monitoring. Homologous red blood cells were given on pump for a hematocrit of less than 0.20 or after CPB for volume requirements if the hemoglobin level was less than 80 g/L.

Platelet and leukocyte estimations were carried out on all PRP collections. Platelet and leukocyte yields were calculated by multiplying measured concentrations by the collected volume. Occasional platelet and leukocyte measurements were performed on platelet-poor plasma to control the quality of our technique. Multiple patient hematological and blood gas variables were documented along with measured mediastinal chest tube drainages and use of homologous blood or blood products.

Comparisons between groups were made using the Mann-Whitney U test for continuous variables and χ^2 test for frequency occurrences.

Results

Analyses of our data showed no difference in patient populations between the control and PLP groups when comparing age, sex, duration of CPB, and numerous other population characteristics (Table 1). Statistically significant differences between the two groups were noted in the following variables: mediastinal chest tube drainage was reduced from 788 ± 542 mL in the controls to 425 ± 207 mL in the PLP group ($p < 0.01$). Fewer units of homologous blood products were transfused in the PLP group ($p < 0.01$). Arterial oxygen tension on extubation was higher in the PLP group (119 ± 25 mm Hg compared with 94 ± 32 mm Hg; $p < 0.01$). Eleven patients in the control group and none of the patients in the PLP group

Table 2. Characteristics of Platelet-Rich and Platelet-Poor Plasma[a]

Variable	Value
PRP volume collected (mL)	857 ± 359
PRP platelet count ($\times 10^3/\mu L$)	462 ± 240
Platelet yield in PRP (vol × platelet count)	$3.5 \times 10^{11} \pm 1.4 \times 10^{11}$
WBC count in PRP ($\times 10^3/\mu L$)	4.5 ± 2.6
WBC yield (vol × WBC count)	$3.4 \times 10^9 \pm 1.9 \times 10^9$
PPP volume (mL)	2571 ± 1062
Platelet count in PPP ($\times 10^3/mm^3$)	7.4 ± 1.3
WBC count in PPP ($\times 10^3/mm^3$)	0.1 ± 0

[a] All values are shown as mean ± standard deviation.

PPP = platelet-poor plasma; PRP = platelet-rich plasma; WBC = white blood cell.

had an arterial oxygen tension less than 75 mm Hg with an inspired oxygen fraction of 0.50 after extubation ($p < 0.01$). The results are summarized in Tables 1 and 2.

Comment

In a recent study Boldt and associates [10] withdrew 10 mL/kg of unconcentrated PRP before CPB and documented multiple variables during and after operation. They found a significant reduction in blood loss (from 696 mL to 500 mL) but no difference in postoperative pulmonary function. They also showed that PRP harvesting significantly decreased the level of elastase, a neutrophil-derived enzyme released from lysosomes that has been implicated as a cause of pulmonary damage [13] and abnormalities of the coagulation and fibrinolytic system [14]. However, on examining their data there was minimal deterioration in lung function in their control versus plasmapheresis groups, and pulmonary shunt fraction was normal in all groups on the first postoperative day. Clearly pulmonary dysfunction was absent in their control group, and therefore no improvement in lung function was achieved with plasmapheresis. In contrast, we commonly see deterioration in lung function, especially in high-risk patients such as the elderly and those with concomitant lung disease and diminished myocardial reserve. Therefore, high-risk patients were not excluded from our study as was the case in previous plasmapheresis studies.

In contrast with the study by Boldt and associates, we found a much greater reduction in mediastinal chest tube drainage (46% compared with 28%) and a significant improvement in pulmonary function in the PLP group. The reduction in mediastinal chest tube drainage occurred without the use of homologous coagulation products. Additionally, the resternotomy rate for excessive postoperative bleeding was decreased. To date we have performed PLP on 60 patients undergoing coronary artery bypass grafting, and none have required resternotomy for bleeding. On the other hand, in the first 4 months of 1991, 6.7% of 160 patients undergoing coronary artery bypass grafting who did not have PLP had resternotomy for bleeding ($p < 0.05$). We surmise that those patients having PLP may be more capable of healing damaged blood vessels because of improved platelet function with less disturbance of their coagulation and fibrinolytic systems. This reduction in resternotomy, if sustained, will realize large cost savings along with reductions in morbidity and improvement in the margin of safety of cardiac surgery.

It is well established that a systemic inflammatory response follows CPB. The trigger for this response is most likely the exposure of blood to abnormal surfaces. Activated platelets transform from a smooth discoid shape to an adherent tenticular form. Widespread capillary microembolism occurs with fibrin-platelet aggregates [15–17]. There is associated activation of the humoral amplification system. This includes the coagulation cascade, the kallikrein system, the fibrinolytic system, and the complement cascade [1–8]. Activated complement further stimulates leukocyte activation. It appears that neutrophil sequestration in pulmonary capillaries is an important accompaniment of lung damage. Pulmonary reperfusion may be a critical period associated with increased neutrophil sequestration in the lungs, where they release highly toxic oxygen free radicals and lysosomal enzymes [13, 18]. Although the morbidity associated with CPB is generally short lived, clinical and biochemical evidence of impaired pulmonary function, extravascular fluid accumulation, renal and neurological impairment, hyperthermia, and coagulopathy is common [1, 2, 4]. Many of the deaths associated with heart operations are due to pulmonary insufficiency and follow prolonged periods of ventilator dependency. The patients at most risk are those at the extremes of age, particularly those with preexisting pulmonary disease and those incapable of increasing myocardial performance [1]. Our findings show that postoperative coagulopathy and pulmonary dysfunction can be alleviated by PLP, presumably because of the prevention of activation and subsequent consumption of those cells removed with the PLP process.

Our method of collection of PRP was fundamentally different from those previously described [10–12]. We processed between 3 and 6 L of blood and separated it into three components: platelet-poor plasma, PRP, and red blood cells. The platelet-poor plasma and red blood cells were pooled and immediately returned to the patient. The mean PRP yield of platelets was 3.5×10^{11}. This represents approximately 25% of the circulating platelets and is harvested more efficiently than the yields of 2 to 3×10^{11} obtained from more expensive and time-consuming machinery used in blood bank single-donor platelet collections. This increase in platelet yield was possible because we also harvested the leukocyte-rich buffy coat containing 3.4×10^9 leukocytes. This is approximately 11% of circulating leukocytes. The contamination of PRP with leukocytes and red cells is unacceptable in blood banking practice for homologous donation. However, for our purposes high yields of leukocytes and substantial red blood cell contamination in our short-term autologous PRP preparation was advantageous. There is a limit to the volume of plasma that can be removed safely from a patient without producing either hypovolemia, hypotension, or excessive need for replacement fluids, which may lead to postbypass overload when PRP is reinfused. To both circumvent these problems and achieve the desired high cellular yields it was necessary to remove only concentrated volumes of plasma.

We feel obliged to caution the reader concerning the potential problems that can arise with the use of historical controls in clinical research. On the other hand, because controls and treatment group patients were studied in the same hospital with the same surgeons within 2 months of each other, these standard problems are minimized.

In conclusion, we have demonstrated that the harvesting of platelets and leukocytes before CPB with subsequent reinfusion after CPB results in reduced postoperative bleeding, a decreased need for homologous blood products, and improved pulmonary function. We believe the improvement in pulmonary function reflects an alleviation of the systemic inflammatory response that can cause multiple organ dysfunction and prolonged morbidity and mortality with cardiac operations.

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New Method for Describing the Performance of Cardiac Surgery Cannulas

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Cardiac surgery cannulas are characterized by external diameter only, which provides little information about the pressure–flow characteristics of a cannula. A system has been developed to describe pressure–flow characteristics with a single, unitless number, M, which is patterned after a Reynolds friction factor correlation. A cannula with a lower M number has a more favorable pressure–flow relationship. The M number was determined for 16 arterial cannulas ranging in size from 10F to 26F and 27 venous cannulas sized 12F to 36F. Pressure–flow characteristics vary considerably among cannulas from different manufacturers despite having similar French sizes. Clinical decisions regarding choice of cannula can be simplified by using the M number, which gives a more accurate description of the performance characteristics of a cannula than the French size designation.

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Arterial and venous cannulas used in cardiac surgery are usually described by French size designation. This describes only the external diameter of the cannula and provides no information regarding the pressure–flow characteristics of the cannula. The performance characteristics of a cannula are determined not only by the diameter but also by the length and the presence of side holes, bends, and fluctuations in the inner diameter of the cannula. Cannulas of the same outer diameter do not necessarily share the same performance characteristics. This may be particularly relevant in operations involving neonatal patients, in which size limitations may influence the choice of cannulas. It may be helpful in these patients to have information regarding the pressure–flow performance of cannulas of the same size. It is currently difficult to compare the performance characteristics of two cannulas with the same French size. A system has been developed in which a single number, referred to as the M number, can be used to describe the pressure–flow characteristics of a given cannula [1, 2]. The M number is a single, unitless number patterned after a Reynolds number friction factor correlation. This number can be easily determined from the geometry of the cannula if the cannula is a straight tube or from simple pressure–flow measurements by the use of a nomogram that graphically describes the functional relationship between the M number, geometry, and pressure–flow characteristics. The M number can allow easy comparison of performance characteristics between similarly sized cannulas.

Material and Methods

The relationship between pressure, flow, and the M number can be seen in the following equation: $M = \log u^{-0.25} + \log(\Delta P/Q^{1.75}) + \text{constant}$, where u is the viscosity of water or blood, ΔP is the pressure change along the cannula, and Q is the flow rate (mL/min)[1, 2]. If blood has a hematocrit of 0.41, u = 0.03 poise and can be included in the constant. The relationship between cannula dimensions and the M number is expressed in the following equation: $M = \log(L/D_e^{4.75})$, where L is catheter length and D_e is effective diameter [1, 2]. It can be seen from the equation that decreasing the internal diameter or increasing the length of the cannula will raise the M number value. Cannulas with a lower resistance to flow will have smaller M numbers. Conversely, a greater M number correlates with a greater resistance to flow.

The M number can be determined by two different methods. If the cannula is a straight tube with a known, constant inner diameter the M number can be determined directly from the nomogram by lining up the relevant points on the length and diameter axes (Fig 1). The M number can then be read directly on the nomogram. If the cannula has irregular geometry the M number must be determined experimentally.

M numbers were experimentally determined for 16 arterial (sizes 10F to 26F) and 27 venous cannulas (sizes 12F to 36F) of varying configurations from different manufacturers. The testing apparatus is shown in Figure 2. The cannulas were submerged under a constant level of water to minimize flow changes due to change in catheter position. A centrifugal pump (Bio-Medicus 5420 D, St. Paul, MN) was used to pump water at 20°C at different pressure gradients across the cannulas. The pressure (mm Hg) was measured as close to the inlet of the cannulas as possible with a mercury manometer. An ultrasonic flow meter (T 101 Transonic Systems, Inc, Ithaca, NY) was

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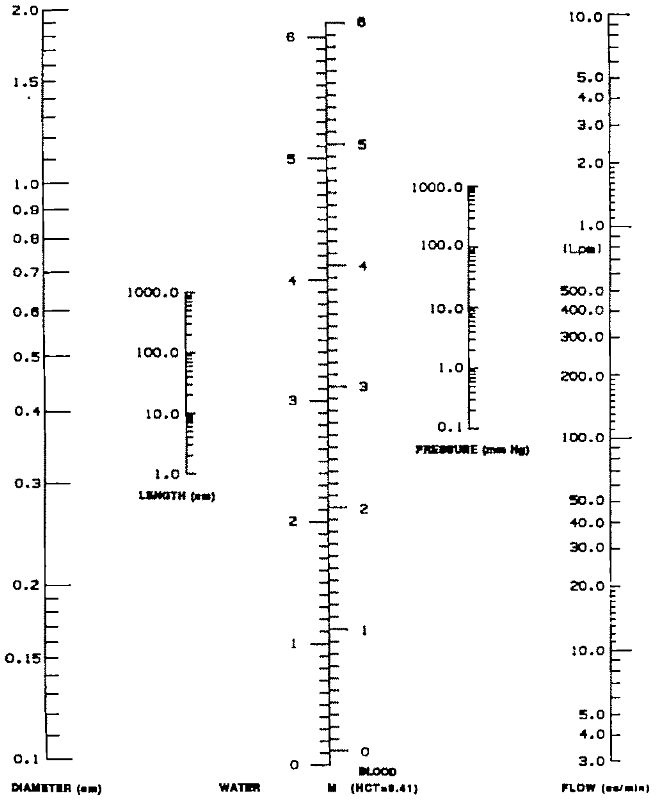

Fig 1. Nomogram for determining M number. If the tubing is straight, has a constant internal diameter, and has no side holes, then the M number can be determined by using the two left axes. Experimentally determined M numbers use the right two axes. (Reprinted from Montoya JP, Merz SI, Bartlett RH. A standardized system for describing flow/pressure relationships in vascular access devices. ASAIO Trans 1991;37:4–8, by permission.)

used to determine the flow rates achieved at a given pressure. For venous cannulas the flow through the circuit was reversed. Flow readings were obtained at several different pressures. Two readings were obtained at each pressure to confirm consistency. The M numbers were obtained from the nomogram for each flow and pressure determination by placing a straight edge across the experimentally determined points. The M number could then be read from the nomogram where the straight edge intersected the M number axis. The M number assigned to each cannula was the average of the M numbers determined at each pressure–flow reading. It should be noted that for each cannula the M number variance at different flow–pressure determinations was less than 0.1. A correction factor in the nomogram allows the determination of the M number with blood (hematocrit, 0.41) or water.

To confirm the clinical utility of the M number, the cardiopulmonary bypass records of 12 pediatric patients were examined. The M numbers were determined by examining the relationship between the pressure across that cannula (line pressure − mean arterial pressure) and the flow rates. These clinically derived M numbers were then compared with experimentally determined M numbers for the same cannula.

Linear regression analysis was used to compare pressure–flow characteristics, M number, and French sizes between the cannulas.

Results

The cannula French sizes, M numbers, and flows at 40 mm Hg pressure are depicted in Tables 1 and 2 for arterial venous cannulas, respectively. It can be seen that there is a wide variation in flow at the same pressure among cannulas of the same French size. As expected, cannulas of similar M number have comparable flow rates at this pressure. This is seen more clearly in Figure 3, which shows that cannulas of the same M number designation have essentially identical flow characteristics, whereas cannulas of the same French size can have widely varying flows at a given pressure. This is further demonstrated in Figures 4 and 5, which show that for venous cannulas of comparable size (20F to 24F) there is excellent correlation between the M numbers and the flow obtained at 40 mm Hg pressure ($r^2 = 0.99$; $p < 0.01$). Conversely, for the same cannulas there is essentially no correlation between French size designation and flow rates at the same pressure ($r^2 = 0.12$; $p > 0.05$). This demonstrates that French size designation is a relatively poor predictor of cannula performance and that a cannula of a smaller French size may have superior pressure–flow characteristics when compared with a cannula of a larger French size. It should be noted that the M number was

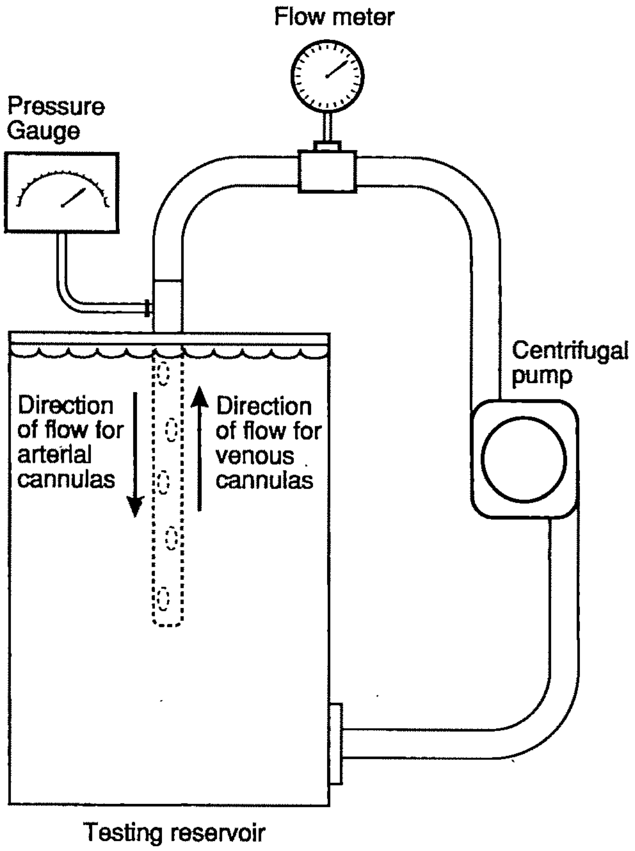
Flow meter
Pressure Gauge
Centrifugal pump
Direction of flow for arterial cannulas
Direction of flow for venous cannulas
Testing reservoir

Fig 2. Diagram of the apparatus used for M number measurement.

essentially the same whether a pressure gradient of 40, 60, or 80 mm Hg was used to experimentally determine the M number. At higher pressures a higher flow rate is obtained, but the nomogram corrects for this and provides the same M number. Therefore, the M number is applicable at all clinically relevant pressure gradients and flow rates.

The clinically derived data for three pediatric-sized cannulas are shown in Table 3. There was good correlation between the clinically and experimentally derived M numbers. The clinical M numbers are typically 0.1 to 0.2 greater than the experimental M numbers, possibly due to hypothermia causing an increase in blood viscosity. However, the relationship between different cannulas is not changed by the apparent change in viscosity; a cannula that has better pressure–flow characteristics (ie, a lower M number) at 37°C compared with another cannula will also have better flow characteristics at 20°C.

Comment

Important determinants of flow through a cannula include internal diameter, presence of side holes, shape, and length. The French size is a useful designation of the outside diameter of a cannula but gives no information regarding performance of the cannula. Many cannulas have thick walls and perform at the level of smaller, thin-walled cannulas. With the M number, the flow of any cannula can be predicted for any given pressure gradient, or conversely, the pressure across a cannula can be predicted at any given flow.

Studies have suggested that the pressure across a cannula should be less than 100 mm Hg to minimize the possibility of blowout and to perhaps minimize hemolysis [3]. The flow obtained through an extracorporeal circuit is in part dependent on the flow capacity of the venous cannulas. Therefore, knowledge of the pressure–flow characteristics is at least as important as knowledge of the French size.

Table 1. Arterial Cannulas

Manufacturer	Size (F)	M Number	Flow (L/min) at 40 mm Hg
DLP 70010	10	3.90	0.79
THI	10	4.25	0.50
USCI 1855	12	4.65	0.28
Polystan 461400	14	3.75	0.96
THI	14	3.75	0.94
THI	16	3.60	1.22
USCI 1857	16	3.25	1.84
USCI 1855	16	4.00	0.68
USCI 1855	18	3.70	1.02
USCI 1858	18	2.95	2.70
THI	18	3.10	2.28
USCI 1858	20	2.90	3.26
THI	21	2.80	3.04
USCI 1858	22	2.60	4.34
USCI 1061	22	3.05	2.57
THI	26	2.55	4.74

Table 2. Venous Cannulas

Manufacturer	Size (F)	M Number	Flow (L/min) at 40 mm Hg
DLP 67312	12	4.05	0.68
USCI 1968	12	4.40	0.42
USCI 1968	14	4.10	0.63
DLP 67316	16	3.45	1.41
USCI 1968	16	3.85	1.18
Sarns	16	3.55	1.34
Polystan 060018	18	3.65	1.18
Polystan 100183	18	3.60	1.24
DLP 67320	20	3.15	2.19
USCI 1968	20	3.35	1.69
Sarns	20	2.75	3.70
Polystan 060021	21	3.30	1.81
Polystan 100213	21	3.30	1.81
USCI 1967SP	22	3.30	1.87
USCI 1968	22	3.15	2.26
USCI 1856	22	3.20	2.15
USCI 1968	24	3.05	2.62
DLP 69324	24	2.45	5.09
Polystan 060024	24	3.10	2.37
Polystan 100244	24	3.10	2.40
USCI 1856	26	2.85	3.37
USCI 1967	26	2.95	2.83
USCI 1856	28	2.65	4.25
USCI 1967SP	30	2.45	5.27
USCI 1856	30	2.45	5.12
USCI 1856	36	2.20	7.70
USCI 1967SR	36	2.10	8.60

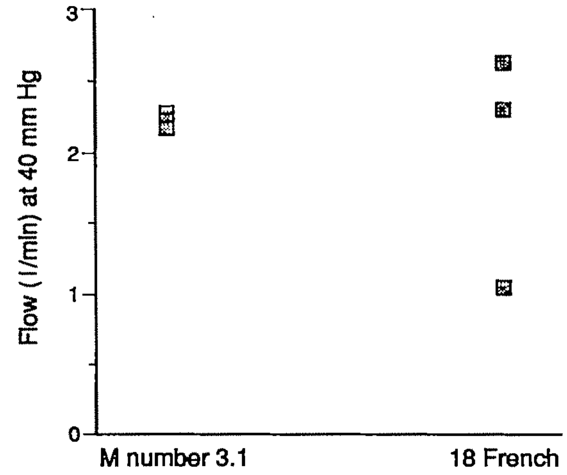

Fig 3. Comparison of M number and French size designation as a predictor of flow at a given pressure.

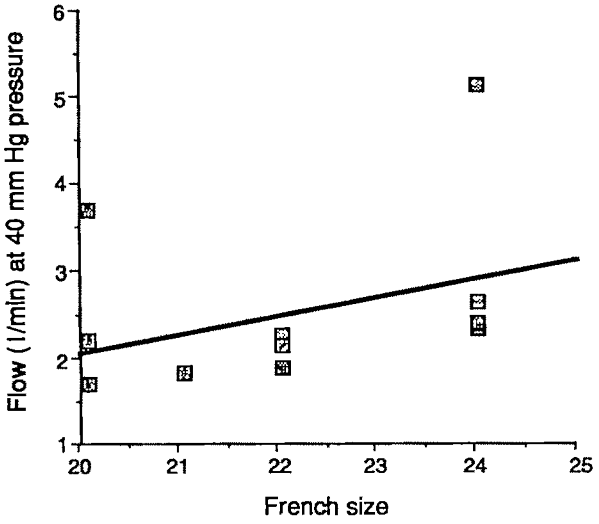

Fig 4. Correlation between French size and flow rate at 40 mm Hg pressure for venous cannulas sized 20F to 24F ($r^2 = 0.12$; $p > 0.05$).

Brodman and associates [3] have demonstrated that there is only a weak correlation between French sizes and pressure–flow performance for arterial cannulas sized 18F to 26F. They also showed that there is a wide variability in performance in cannulas of comparable size. This study also demonstrated that there is relatively poor correlation between performance of arterial and venous cannulas and French size designation. The M number, as expected, correlated very closely with pressure–flow performance. The M number reliably describes cannula performance with a single number, allowing easy comparison of different cannulas.

The clinical data obtained in this study show that the M number obtained in the laboratory with water under ideal conditions correlates closely with the clinical performance of the cannula. The M number of a cannula is easy to determine, and testing could be economically performed by manufacturers for each cannula size and configuration. The following case study illustrates the potential usefulness of the M number. A 5-month-old, 6.4 kg infant with a ventricular septal defect is undergoing primary repair of the cardiac defect. A 10F cannula is used for aortic perfusion. The initial bypass flow is 750 mL/min, with a line pressure of 250 mm Hg. The perfusionist notes that the line pressure is relatively high, and a quick glance at the tubing and cannula reveals no kinks. A suggestion is made that the cannula is too small for the flow rate. The M number of the cannula is 4.30. With a flow of 750 mL/min the expected pressure across the cannula would be approximately 110 mm Hg, which would result in a line pressure of 160 mm Hg if the mean arterial pressure was 50 mm Hg. The cannula does appear to be appropriately sized. The pressure drop across the cannula is much greater than would be expected, suggesting that the position of the cannula is at fault. The cannula is repositioned and the line pressure drops to 165 mm Hg. The rest of the procedure proceeds uneventfully.

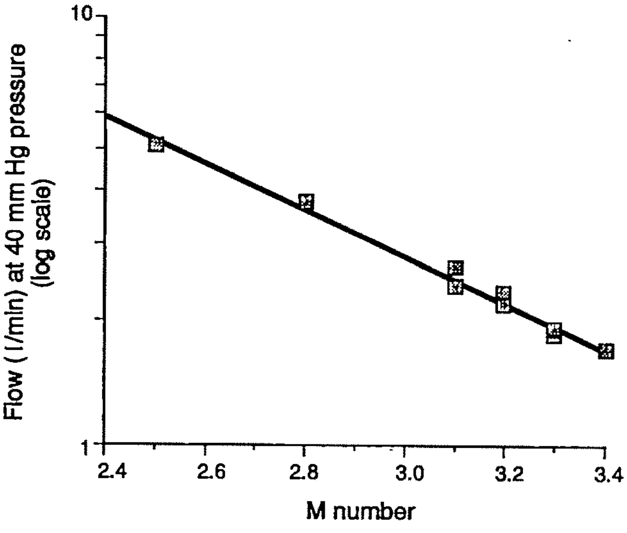

Fig 5. Correlation between M number and flow rate (log scale) at 40 mm Hg pressure for venous cannulas sized 20F to 24F ($r^2 = 0.99$; $p < 0.01$).

Table 3. Comparison Between Clinical Cannula Performance and Experimentally Derived M Numbers

Size (F)	Clinical M Number[a]	Experimental M Number
10	4.40	4.35
14	3.90	3.75
18	3.40	3.15

[a] n = 4 for each cannula size.

The M number is a new system to describe the performance of surgical cannulas. It is easy to determine and gives useful information regarding the pressure–flow characteristics of any cannula. Widespread acceptance of the M number by cannula manufacturers would allow surgeons to easily compare the performance of different cannulas and, in conjunction with size, would simplify selection of the appropriate cannulas for the particular needs of the operation.

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Experience With the Symbion Total Artificial Heart as a Bridge to Transplantation

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From December 1985 through January 1991, 9 patients underwent bridging to transplantation using a Symbion J-7-70 total artificial heart. There were 4 female and 5 male patients aged 31 ± 14 years (range, 15 to 52 years). Five patients were supported on an intraaortic balloon pump before total artificial heart support, and 2 had biventricular assist devices as well. Total artificial heart support was maintained for 17 ± 12 days (range, 4 to 44 days); all patients underwent transplantation. Three patients died after transplantation on day 0 (primary donor organ failure), 25 (acute rejection), and 256 (multiorgan failure). The remainder were discharged at 41 ± 32 days (range, 13 to 101 days). One patient died 28 months after transplantation of late acute rejection. Actuarial 1-year and 3-year survival is 67% and 55%. There were no surgical wound infections. Problems encountered in the J-7-70 period and the period after transplantation were for the most part related to patient condition in the period before implantation. The Symbion J-7-70 total artificial heart is an effective device for total circulatory support in patients with end-stage cardiogenic shock when an organ donor is not available. Organ system failure and infection before implantation may persist into the transplantation period resulting in long-term complications, increased mortality, and prolonged hospital stay; therefore, early implantation of the device when indicated should be applied.

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The first attempt to bridge a patient to cardiac transplantation occurred in 1969 when Cooley and associates [1] used the Liotta heart. Successful circulatory support and transplantation occurred but the patient died in the early period after transplantation. This experience documented that total hemodynamic support could be obtained with an artificial device replacing both ventricles. Thirteen years later, DeVries and colleagues [2, 3] attempted cardiac replacement on a permanent basis using the Symbion J-7-100 (Jarvik-7) total artificial heart (TAH). Long-term survival was obtained but all patients who received permanent implants suffered major complications and died. Copeland and associates [4, 5] for the first time successfully used a TAH as a bridge to transplantation, ushering in an era of heightened enthusiasm for the use of total circulatory support in critically ill patients. Although permanent replacement has not been realized, the use of a TAH as a bridge has become firmly established.

Multiple models of TAH have been used as bridge devices (Table 1); however, only the Symbion J-7 and more recently the Vienna heart have resulted in substantial long-term survival. Since 1985 the Symbion TAH has been used more than 170 times [6]. Shifts in research interest to the use of sophisticated univentricular and biventricular support devices and the Food and Drug Administration restrictions on the manufacture and shipping of the Symbion device have recently diminished the frequency of its use. This report documents the total experience at the Minneapolis Heart Institute using the Symbion J-7-70 as a bridge to transplantation. Patients' complications and adverse events were recorded during the preoperative, implantation, and posttransplantation periods. This examination was made in an attempt to differentiate secondary events that arose during each of the above periods from directly device-related problems.

Material and Methods

The hospital charts of all patients were reviewed to obtain details of the bridging and the patient's hospital course. Indications for implantation included candidacy for transplantation with regard to pulmonary vascular resistance and negative cytotoxic screen coupled with refractory cardiogenic shock after exhaustion of other forms of circulatory support therapy. The TAH was not used as a resuscitative device except in 1 case in which a patient who had been previously selected suffered cardiac arrest. The Symbion J-7 devices have been previously described [7]. Surgical technique for implantation is similar to that of Levinson and Copeland [8] with the exception that fibrin sealant [9] was used on all suture lines to prevent bleeding. Anticoagulation was begun 12 to 24 hours after implantation when chest tube output was less than 50 mL/h and consisted of increasing dosages of intravenous heparin to maintain thrombin time between 20 and 40 seconds at 1:4 dilution. Dipyridamole (Persantine; Boehringer Ingelheim, Ridgefield, CT) was also added when

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Table 1. Models of Artificial Hearts Used as Bridges to Transplantation[a]

Model	N (percent transplanted)	Survival
Liotta	1 (100)	–
Askutsu	1 (100)	–
Phoenix	1 (100)	–
Symbion J-7-70	141 (70)	+
Symbion J-7-100	34 (62)	+
Berlin	7 (43)	–
Unger/Ellipsoid	4 (75)	–
Penn State	3 (67)	–
Vienna	2 (100)	+
Moscow Poisk	12 (?)	?
Czech	6 (0)	–

[a] Johnson et al 1991 [6].

platelet function returned to normal. Most patients were not immediately listed for priority transplantation. Our philosophy has been consistent with that of Griffith [10] in that several days were cleared for patient recovery from operation and any secondary organ system dysfunction that might be present. Outpatient records documented follow-up, which is 100%.

Immunosuppressive regimens have been described previously [11]. Briefly, standard triple-drug therapy was used for the first 2 patients; however, in May 1987 a regimen of OKT3 induction with steroid-free maintenance immunosuppression was initiated under the philosophy of minimizing posttransplantation toxic manifestations of these agents in critically ill patients and sparing the long-term side effects of steroids. The regimen used in 7 patients is shown in Table 2.

Actuarial calculations were performed using the Kaplan-Meier technique. Linearized continuous data are expressed as mean ± standard deviation.

Results

From December 1985 through December 1990, a total of 9 patients (4 were female and 5, male) underwent cardiac transplantation at the Minneapolis Heart Institute, preceded by the use of the Symbion J-7-70 TAH as a bridging device. The demographic data and patient characteristics before implantation are listed in Table 3. The mean patient age was 31 ± 14 years (range, 15 to 52 years). The cause of the underlying heart disease was idiopathic cardiomyopathy (in 3 patients), acute viral cardiomyopathy in 2, and ischemic heart disease, rheumatic heart disease, giant cell myocarditis, and idiopathic hypertrophic cardiomyopathy in 1 patient each.

Events occurring before implantation are delineated in Table 3. Five patients were in cardiogenic shock before device implantation. Three patients had operation immediately before device placement. One patient could not be weaned from bypass after a coronary artery bypass graft operation, and 2 patients (one heart transplant, one valve replacement) were supported on biventricular assist devices for 12 hours and 4 days, respectively, before TAH implantation. All patients but 1 were on inotropic support. A 15-year-old patient was placed emergently on cardiopulmonary bypass while cardiopulmonary resuscitation was being performed and underwent J-7-70 implantation. He had been selected for TAH use before cardiac arrest. Six patients had an intraaortic balloon pump placed before the TAH (2 had biventricular assist devices).

Table 2. Immunosuppression Regimens

Drug	TDI (n = 2)	OKT3 (n = 7)
Cyclosporine		
Pretransplantation	4 mg/kg	0–4 mg/kg[a]
Posttransplantation	$3\text{–}5\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ po Levels: 200 ± 25 ng/mL 6 wk 150 ± 25 ng/mL 6–26 wk 100 ± 25 ng/mL 1–6 mo	$1\text{–}5\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ po Level[b], 0–100 ng/mL posttransplant weeks 1–2 then as TDI
Azathioprine	$1.5\text{–}3\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ po WBC = 3,000–5,000/μL	Same
OKT3	None	5 mg/day from POD 2 to 15
Methylprednisolone	500 mg IV bolus after CPB then 125 mg IV q 12 h × 3 doses	Same Same, 250 mg IV bolus on POD 15
Prednisone	1.5 mg/kg (first dose) po, taper to 0.5 mg/kg by 1 mo, to 0.15 mg/kg by 6 mo, and to 0.1 mg/kg at 1 year	$0.15\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ POD 2–14, 1.5 mg/kg on POD 16, tapered to 0.5 mg/kg by 10 days then 2.5 mg/wk to discontinuation
Dopamine	$1\ \mathrm{mg \cdot kg^{-1} \cdot min^{-1}}$ for 1 wk IV	$1\ \mathrm{mg \cdot kg^{-1} \cdot min^{-1}}$ for 1 wk IV

[a] Pending renal function. [b] Whole blood 12-hour trough level as measured by high-performance liquid chromotography.

CPB = cardiopulmonary bypass; IV = intravenously; po = per oral; POD = postoperative day; IDI = triple-drug immunosuppression; WBC = white blood cell count.

Table 3. Patient Demographics Before Symbion J-7-70 Implantation

Variable	1	2	3	4	5	6	7	8	9
Age (y)	40	28	15	50	45	19	16	19	52
Sex	F	F	M	M	F	M	M	M	F
Height (cm)	154	161	163	182	152	170	180	187	162
Weight (kg)	55	63	46	94	48	69	66	86	57
Cause	Postviral	Giant cell myocarditis	IDC	Ischemic cardiomyopathy	RHD	Congenital hypertrophic myopathy	Postviral	IDC	IDC
Indication	Cardiogenic shock	Cardiogenic shock	Cardiogenic shock	Failure to wean CPB	Failure to wean VAD	Donor organ failure	Cardiogenic shock	Cardiogenic shock	Cardiogenic shock
Pre–J-7-70 support	Inotropic, IABP	Inotropic	Emergent CPB	Inotropic, IABP	Inotropic, IABP, BIVAD	Intropic, BIVAD, IABP	Inotropic	Inotropic, IABP	Inotropic, IABP
Pre–J-7-70 organ dysfunction	Renal, leg ischemia	–	Renal, neurologic	–	Respiratory	–	–	Superior caval thrombosis	Pulmonary infiltrate, respiratory

CPB = cardiopulmonary bypass; IDC = idiopathic dilated cardiomyopathy; RHD = rheumatic heart disease.

Three of 9 patients had organ system dysfunction of the kidneys (2) or lung (2) and an embolic cerebrovascular accident (1) before implantation. One patient had acute superior vena cava thrombosis. Four patients had moderate to severe cognitive disturbance before TAH implant. Two were mildly impaired. Three others were anesthetized from a prior operation or on VAD support.

In all cases, the TAH sustained life until a suitable donor heart was found and transplanted. No patient died while on the J-7-70. The mean time spent on TAH support was 17 ± 12 days, with a range of 4 to 44 days. Surprisingly few complications directly related to the device and implant period occurred. These are detailed in Table 4. Two patients required prolonged ventilator support, but ventilatory difficulties were related to preoperative deterioration with severe cardiogenic shock in 1 and a preoperative embolic stroke with cardiac arrest in a second. There were no device failures or evidence of hemolysis. Although there were no mediastinal surgical wound infections, infectious complications developed in 4 patients. Two of these were nonascending drive line infections with *Staphylococcus aureus*. One further patient on biventricular support for 4 days before implantation had development of positive blood cultures while on the TAH and was found to have enterococcus from the mediastinum, urine, driveline and the central venous pressure tip as well. Positive blood cultures for *Serratia*, the source of which remains unknown, developed in a fourth patient. None of these infections affected the pretransplantation or posttransplantation course. One patient with renal failure before implantation required dialysis, and neurologic symptoms developed in 2 patients while they were on the J-7-70. One patient had a transient right hemispheric visual disturbance, and a second had a prolonged episode of confusion, aphasia, and incontinence. Although both episodes resolved, the latter resulted in catatonia for several days of TAH support which persisted in the period after transplantation. Because of immobility of this patient, a sacral decubitus ulcer developed and required flap closure after transplantation. One patient required prolonged ventilator support because of preimplantation embolic cerebrovascular accident and cardiac arrest. He was extubated and reintubated three times during his 25-day implantation for a total of 21 ventilator-dependent days. The patient with the most complications, our first, suffered severe multiorgan failure before implantation from cardiogenic shock; multiple complications developed after implantation from which she never recovered over the 256-day posttransplantation course (see Table 4). Over the time of implantation, leg ischemia from intraaortic balloon pump placement and renal, respiratory, and hepatic failure were persistent and peptic ulcer disease arose with the development of pancreatitis and pancreatic pseudocyst formation later requiring operation. These problems persisted into the period after transplantation and, coupled with intermittent infectious processes (cytomegalovirus, *Pneumocystis*, *Pseudomonas*), resulted in the patient's death of multiorgan system failure [12].

After completion of the implant procedure, meticulous hemostasis was obtained and patients were observed in the operating room for several hours. Over the first 48 hours, the average blood replacement was 6.8 units with a range of 2 to 19 units. One patient was returned to the operating room during this period. Two others were returned for evacuation of a mediastinal hematoma on the fifth and sixth days after implantation, respectively.

Three patients died during their posttransplantation hospitalization (Table 5). The first patient died of sepsis-

Table 4. Complications on J-7-70 Support

Variable	1	2	3	4	5	6	7	8	9
Implant duration (d)	44	4	25	17	5	18	15	25	7
Ventilator (d)	20	1	21	1	4	1	1	1	1
Blood loss in 48 h (U)	19	5	11	8	2	3	2	2	9
Surgical wound infection	–	–	–	–	–	–	–	–	–
Other infection	Driveline	–	–	–	Blood, CVP, driveline, urine, mediastinum	–	–	Driveline	Blood, pneumonia
Dialysis	+	–	–	–	–	–	–	–	–
Stroke	–	–	–	TIA	–	–	–	Confusion, TIA	–
Hemolysis	–	–	–	–	–	–	–	–	–
Reop for bleeding	Early	–	–	–	–	Late	Late	–	–
Device malfunction	–	–	–	–	–	–	–	–	–
Other	PUD, pancreatic pseudocyst	–	Prolonged ventilator support	–	–	–	–	Catatonia, sacral decubitus	Pneumonia

CVP = central venous pressure tip; PUD = peptic ulcer disease; TIA = transient ischemic accident.

associated multiple organ system failure at 256 days after transplantation after a protracted postoperative course [12]. A second patient died of acute rejection at 28 days after transplantation [11]. The third patient death occurred on the day of transplantation and was due to primary donor organ failure after a difficult donor organ implantation when severe weather delayed return of the donor organ. Right heart failure occurred during the early

Table 5. Posttransplantation Course

Variable	1	2	3	4	5	6	7	8	9
Survival at 1 mo	+	+	+	+	–[a]	+	+	+[a]	–[a]
Survival at 3 mo	+	+	+	+	NA	+	+	+	NA
Survival at 1 y	–[a]	+	+	+	NA	+	+	+	NA
Posttransplantation survival (mo)	9[b]	29[b]	46	44	1[b]	34	33	26	0[b]
Rejection (days after transplantation)	–	6,38,854	367	–	23	–	–	–	NA
Infections at 1 y	CMV, pneumonitis, *Pneumocystis*, *Pseudomonas* sepsis	–	Mumps	–	NA	–	–	Sacral ulcer, confusion	NA
Other complications	Leg ischemia, multiorgan failure	–	Ganciclovir leukopenia	–	NA	–	–	BVAD support of donor heart	NA
Current steroids	NA	NA	–	–	NA	–	–	–	NA
Posttransplantation	[256]	11	139	17	[28]	17	15	63	1[a]

[a] Died during hospitalization after transplantation. [b] Late death.

BVAD = biventricular assist device; CMV = cytomegalovirus; NA = not available.

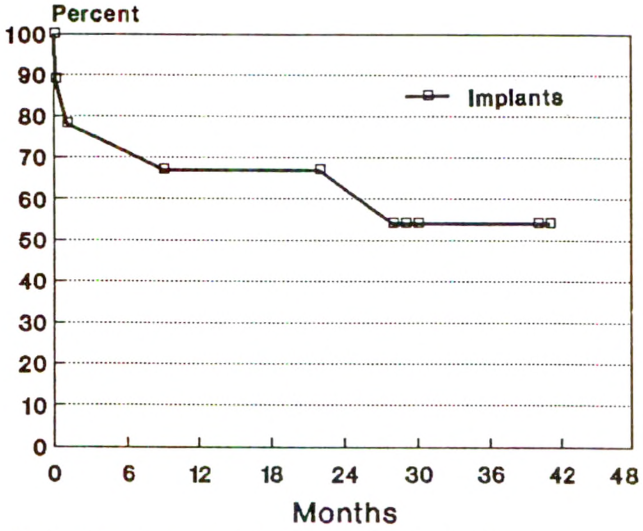

Fig 1. Actuarial survival of patients undergoing bridging to transplantation using the Symbion J-7-70 total artificial heart.

postoperative period and was rapidly followed by cardiac arrest. One patient required use of an intraaortic balloon pump and biventricular assist device for support of cardiac function for 4 days after transplantation. He was discharged on the 63rd day after transplantation and remains well [13]. The remainder were discharged at 36 ± 23 days (range, 13 to 73 days) after transplantation. One patient died of late acute rejection at 28 months after transplantation following treatment. The remaining 5 patients are in functional status 1 at 23, 30, 31, 41, and 42 months. The 30-day, 1-year, and 3-year actuarial survival rates were 78%, 67%, and 55% respectively (Fig 1).

Rejection was seen in three patients (33%). One patient had rebound acute rejection after OKT3 therapy. From this time a protocol of a steroid bolus followed by slow tapering of steroids after OKT3 therapy was instituted [11]. One patient (who did not receive OKT3) had three rejection episodes on days 6, 38, and 854 after transplantation. Each responded to steroid therapy, but the patient died after the last rejection episode. A third patient (OKT3) had a rejection episode more than a year after transplantation (see Table 5) treated with steroid taper. Bacterial infection was a major cause of morbidity, but none of the infections were related to the surgical wound. One patient had a protracted postoperative course with multiple processes [12]. Another patient had *Enterobacter* pneumonia. Both of these patients died before discharge in the posttransplantation period, but not of infection. No other bacterial infections were seen in these patients during the posttransplantation period. Posttransplantation cytomegalovirus infection was seen in 3 patients (33%), and 2 patients suffered herpes simplex virus infections (22%). Of the 5 patients alive, one has a pre-TAH neurologic deficit. The remainder are in functional status 1, and all surviving patients are free of steroids.

Comment

The shift of direction in cardiovascular research to the use of univentricular support devices coupled with the recent FDA suspension of the Symbion TAH have severely limited the use and availability of the TAH. In 1990 only 14 devices were implanted worldwide [6]. Yet, it is apparent from our experience with an absence of mortality related to circulatory failure during device implantation that the TAH successfully maintains vital functions and allows successful transplantation in all cases. It is also of interest that most major complications occurring over the patient's entire hospital course emanated from preexisting complications or debilitation due to cardiogenic shock before implantation [14]. In those cases in which the TAH was implanted while the patient was free of organ system dysfunction, complications relating to the device were relatively few. This would indicate the factors relating to organ recovery are progressive and not related to the TAH, similar to data reported by others [15]. Mortality after transplantation was high, with 3 patients (33%) dying before discharge from the hospital. It was apparent from our experience that the better the preoperative condition of the patient before TAH implantation, the more benign the postoperative course [16, 17]. Operative survivors with organ system dysfunction before implantation (n = 3) required an average hospital stay of 153 days after transplantation; there was one death in this group. For patients with no preoperative organ system dysfunction or infection (n = 4) the average hospital stay after transplantation was 15 days. Two other patients with complications before implantation died in the operative period. Age in and of itself was not a factor in survival as in the experience of others [16]. Yet it is apparent that younger patients have more reserve to tolerate multiple surgical procedures.

The formation of extensive adhesions may occur over a short period of time, and as previously noted, may make explantation of the Symbion device difficult as well as complicate the implantation of the donor organ [18]. This occurred in 1 of our patients and posttransplantation intraaortic balloon pump and ventricular assist device support was required. The use of continued forms of mechanical support of the donor heart after transplantation has been successful and allowed long-term survival [13].

With the high incidence of complications extending into the period after transplantation, coupled with the usually prolonged recovery after multiple surgical procedures, minimizing the additional toxic side effects of immunosuppressive agents is highly desirable if secondary organ system dysfunction and sepsis are to be prevented [10, 11]. To accomplish this an induction protocol using OKT3 monoclonal antibody was devised and used in 7 of 9 patients [11]. Although OKT3 has in itself some undesirable side effects, most are associated with the first and second dosages and dramatically decrease thereafter. Those early side effects can effectively be minimized by withholding the first administration until the patient is within 10% of dry weight and by pretreatment with antihistamines, hydrocortisone, acetaminophen, and ranitidine. Use of this powerful agent early in the posttransplantation period has allowed the dosage of other immunosuppressive agents to be minimized. No rejection episodes have been seen during OKT3 administration in this group or in a larger group of high-risk patients managed similarly [19]. OKT3 has become our first-choice immunotherapy for all patients bridged to transplantation, as well as for all high-risk transplant patients. Although rejection was not seen in any patient during OKT3 administration, 1 patient died of rebound rejection on posttransplantation day 28. This patient was not given steroids after the OKT3 course because of concern for mediastinal contamination, and is described in detail elsewhere [20].

To further prevent the development of pulmonary infection and sepsis we, as others, attempt to extubate patients as early as possible after implantation or transplantation [16]. Only patients with organ system dysfunction before implantation required prolonged ventilator support (see Table 3). Infection was not a cause of early posttransplantation mortality in our series [16, 21]. On long-term follow-up, steroid-related complications in all surviving patients have been eliminated as none are taking the drug. All patients are in status 1 from a cardiovascular standpoint, but 1 has a permanent neurological deficit as a consequence of a preimplantation cardiac arrest and cerebrovascular accident. The only late death occurred in a patient who, 28 months after transplantation, suffered late acute rejection and died.

The 30-day survival of 77% and 1-year actuarial survival rate of 67% is not comparable with that achieved in heart transplantation. However, all these patients were premorbid with death imminent. With these results, we believe that the Symbion TAH presents a unique alternative for patients in cardiogenic shock who are eligible for transplantation but have not been able to obtain a donor heart. As the success in heart transplantation continues to improve and the limited resource of donor hearts becomes even more problematic, the need for a bridging device is going to continue to be a factor in determining survival for patients awaiting a heart transplant [10, 22]. Selection of patients is of utmost importance, and early placement of the TAH before the development of multiorgan system dysfunction improves long-term results [18]. We concur with strict selection criteria previously published, which may maximize results [10, 18, 23]. Although a scoring system as described by Pennington and associates [23] is useful for patient selection, such situations are dynamic, and decisions regarding patient selection often must be made rapidly because of declining hemodynamics. Stabilization by additional drug therapy may allow some postponement of device selection, but delayed implantation may result in complications that carry through the bridging period affecting the posttransplantation course or even preclude transplantation once implantation has been accomplished [24]. Additionally, should established organ system dysfunction or infection be present, reversibility is always a question [15]. It may be possible to convert a nontransplant patient into a transplant candidate by the application of circulatory assistance, but higher mortality and morbidity must be accepted if such a decision is made [16, 24]. Although external pressure on the implant team from the patient, family, or attending physician and a "last chance" philosophy may exist, such considerations should not predominate in patient selection. With the availability of multiple types of support systems, the TAH is not suitable for all patients and its use should be individualized, taking into account the availability of other devices, their benefits, and their limits [22, 25, 26]. Yet marginal hemodynamic stability should not exclude a patient from device consideration. Many real and potential complications are accentuated with the use of a TAH [27]. Problems encountered with the initial use of the device including massive bleeding, severe hemolysis, reoperation, renal failure, thromboembolism, sepsis, and others did not affect our patients unless present before implantation and have been infrequent. Importantly, there were no posttransplantation surgical wound infections [28]. The fit of the device is an important factor in function of the device, and the absence of atrial compression must be assured [18, 27].

The Symbion J-7-70 TAH satisfactorily accomplishes a bridge function. Improvements, especially relating to the driving system and power source, should be made to achieve longer, morbidity-free bridging periods and better quality of life while on the device. Easing of strict restrictions by the FDA would benefit researchers pursuing this goal. In spite of restricted availability, these results support the use of the TAH in selected patients as a bridge to transplantation. We concur with the opinions of others that use of the TAH is lifesaving, but in poorly selected patients the course is fraught with complications, one begetting the other, expensive, and potentially wasteful of the scarce resource of a donor heart for an individual with limited potential for survival thus opening the concept of bridging to social criticism [16, 18, 23, 28].

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Gastric Substitution for Resectable Carcinoma of the Esophagus: An Analysis of 368 Cases

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Between 1974 and 1984, 1,188 patients with esophageal malignancies were treated in the Division of Thoracic Surgery of Veterans General Hospital, Taipei. The rate of resectability was 42.6%. Since 1974, the stomach has been used as esophageal substitute, and through 1984, a total of 368 patients were collected. The routes of reconstruction included retrosternal (77.2%), posteromediastinal (7.1%), and intrathoracic (15.7%). The rates of postoperative complications and surgical mortality in these 368 patients were 26.3% and 6.5%, respectively. Leakage of anastomosis was the most frequent complication. The incidence of stricture of esophagogastrostomy was 25.5%. All strictures were relieved by esophageal dilations. An average of 3.9 esophageal dilations were performed per patient (range, 1 to 15). Radical lymph node dissection was not routinely performed in our series. The actuarial 2-year and 5-year survival rates were 26.4% and 7.6%, respectively. Among 76 patients undergoing cervical esophagogastrostomy and surviving for more than 1 year, late complications occurred as follows: acid/bile regurgitation, 46.1%; postprandial fullness of abdomen, 38.2%; dumping syndrome, 13.2%; distended stomach with dyspnea, 11.8%; aspiration pneumonia, 6.6%; and gastric ulcer, 6.6%. Moreover, compared with patients without pyloroplasty, those with pyloroplasty were found to have a higher incidence of bile regurgitation (55.5% versus 8.6%), dumping syndrome (33.3% versus 6.9%), aspiration pneumonia (16.7% versus 3.4%), and gastric ulcer (22.2% versus 1.7%). In studies of total esophageal substitute transit time and technetium 99m-HIDA test (n = 33), we found that pyloroplasty or pyloromyotomy failed to normalize the disturbed gastric emptying but resulted in a high incidence of enterogastric bile reflux. Thus, we conclude that routine pyloroplasty or pyloromyotomy is not necessary. Although more than half of our patients had experience with late complications of gastric transplantation, most of them (>80%) can take care of themselves and their daily work after proper medication and physical therapy, if there is no tumor recurrence or other associated diseases.

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Carcinoma of the esophagus occurs with unfortunate frequency among the Chinese [1–3]. Although operation may provide the only chance of a cure for esophageal carcinoma, results of treatment for symptomatic patients are unsatisfactory despite the availability of new therapeutic modalities. Thus, the aim to relieve symptoms of dysphagia and preserve the functional gastrointestinal continuity is very important in the management of esophageal carcinoma.

As early as 1920, Kirschner [4] suggested mobilization of the stomach for replacement of the esophagus. However, the fear of inadequate length, reduced blood supply after mobilization, reflux esophagitis, and cardiopulmonary disturbances delayed the further development of this method. Consequently, interposition of the colon became widely used. Since Nakayama [5], Akiyama [6], and Wang and associates [7] successfully performed Kirschner's procedure, the stomach has become the most common organ for esophageal substitution after esophagectomy in the past 20 years. The stomach is advantageous for its simplicity and fewer complications when used properly [6–8]. However, little information regarding the function of gastric transplants with a longer follow-up period has been reported in the literature.

This report analyzes our 10-year experience of 368 patients with esophageal carcinoma in whom we used the stomach as an esophageal substitute after resection of esophagus. The late complications of gastric transplantation are also assessed and discussed.

Material and Methods

From January 1974 to December 1984, a total of 1,188 patients with epidermoid carcinoma of the esophagus were admitted to the Division of Thoracic Surgery at Veterans General Hospital, Taipei. Of these 1,188 patients, 506 patients had undergone subtotal esophagectomies, a rate of resectability of 42.6%. Among these 506 patients, the stomach had been used as esophageal substitute after esophagectomy for 368 patients (72.7%).

Generally we resect carcinomas of the upper and middle thirds of the esophagus through a standard right thoracotomy, and we use a left thoracotomy for carcinoma

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of the lower third of the esophagus. Cervical esophagogastrostomy was performed by means of the Kirschner-Nakayama type of gastric tube through the retrosternal route [4–6, 8]. For lesions of the lower esophagus, more than 33 to 34 cm from the incisors, the thoracic esophagus can be resected with an extended left thoracoabdominal incision through the sixth or seventh intercostal space with division of the costal margin and peripheral diaphragmatic detachment, and the stomach is mobilized [9]. The apex of the skeletonized stomach is then brought up through the hiatus and posterior mediastinum, and into the neck for esophagogastrostomy, or an intrathoracic esophagogastrotomy is performed. However, radical lymph node dissection was not routinely performed in the present series. It depended on the surgeons.

For patients with carcinoma involving the upper third of esophagus, preoperative radiotherapy with a total dose of 30 to 40 Gy was completed 1 month before the resection. In addition, postoperative chemotherapy or radiotherapy was instituted for most patients with stage III cancer (according to American Joint Committee for Cancer staging). The combination regimens of chemotherapy consisted of cisplatin, bleomycin, and vindecine or vincristine, or of cyclophosphamide, methotrexate, and bleomycin. The total dose of postoperative irradiation ranged from 50 to 60 Gy, depending on the patient's condition. The postoperative adjuvant therapy was carried out about 1 to 3 months after operation.

A total of 76 patients who had undergone cervical esophagogastrostomy and survived for more than 1 year were available to be followed up with functional evaluation of the gastric transplant. Questionnaires regarding symptoms were administered by a third person. Nevertheless, only 33 of 76 patients could complete the studies of radionuclide esophageal transit time [10–12] and technetium-99m–HIDA ([2,6-dimethyl phenylcarbamoylmethyl] iminodiacetic acid) test [12–14], including 23 patients without pyloroplasty and 10 patients with pyloroplasty. All data were presented as mean ± standard error of the mean. Unpaired t test was used for statistical analysis, and significance was assumed for a p value less than 0.05.

Results

The average age of the 368 patients in whom the stomach was used as an esophageal substitute was 61.6 years, ranging from 29 to 82 years. Only 13 patients were female (3.5%); this is due to the patient population of Veterans General Hospital. The average loss of body weight before admission was 5.2 kg (range, 0 to 25 kg). History of smoking and evidence of chronic pulmonary abnormality occurred in 68.6% and 35.4%, respectively. The histopathological staging and the level of lesions in these 368 patients are shown in Tables 1 and 2. Unfortunately, 89 patients' staging and 12 patients' anatomical site of lesion were not available for evaluation. The most common location of tumor was in the middle third of the esophagus (54.5%), and the most frequent staging was stage III (43.4%).

Table 1. Staging Distribution of Patients With Carcinoma of Esophagus Who Received Esophagectomy and Esophagoplasty With Stomach[a]

Stage	No. of Patients	Percent
I	54	19.4
II	74	26.5
III	121	43.4
IV	30	10.7
Total	279	100.0

[a] Stage was unknown for 89 patients.

Cervical esophagogastrostomy was performed through the retrosternal route for 248 patients (77.2%) and through the posteromediastinal route for 26 patients (7.1%). Intrathoracic esophagogastrostomy was performed through the hiatus for 58 patients (15.7%).

The incidence of postoperative complications and hospital mortality (within 30 days) are presented in Table 3. The various complications occurred in 97 patients, an incidence of 26.3%. Among these 97 patients, 24 patients died in the hospital. Thus, the overall operative mortality rate was 6.5%. The most frequent causes of postoperative death were pulmonary complications and sepsis (72.2%). The early postoperative complication with the highest incidence was anastomotic leakage (47 patients [12.8%]: cervical, 41; intrathoracic, 6). Among the 47 patients with anastomotic leakage, only 3 (6.4%) died of subsequent pulmonary complications and sepsis. Seven patients with carcinoma of the cervical esophagus received preoperative radiotherapy. Postoperative irradiation or chemotherapy or both were routinely performed for most patients with stages III or IV tumors if the patients accepted and could tolerate this further adjuvant therapy. The actuarial 5-year survival rate in our series was 7.6% (28/368 patients), and 2-year survival was 26.4% (97/368 patients).

The delayed postoperative complications included anastomotic stricture and functional disturbance of the gastrointestinal tract. Postoperative anastomotic stricture is defined as evidence of progressive dysphagia, intolerance to soft diet, and a stricture in the esophagogram.

Table 2. Distribution of Tumor Level in Patients With Carcinoma of Esophagus Who Received Esophagectomy and Esophagoplasty With Stomach[a]

Level	No. of Patients	Percent
Cervical esophagus	9	2.5
Upper thoracic esophagus	62	17.4
Middle thoracic esophagus	194	54.5
Lower thoracic esophagus	87	24.4
Abdominal esophagus	4	1.1
Total	356	100.0

[a] Tumor level was unknown for 12 patients.

Table 3. Postoperative Complications and Hospital Mortality in 368 Patients Undergoing Esophageal Resection With Stomach Reconstruction for Carcinoma of Esophagus

Complication	No. of Patients (%)	No. of Deaths (%)
Anastomotic leakage	47 (12.8)	3 (6.4)
Cervical	41 (13.2)	0 (0)
Intrathoracic	6 (10.3)	3 (50)
Wound infection	16 (4.1)	. . .
Pulmonary	20 (5.2)	13 (65.0)
Empyema	9 (2.3)	1 (11.1)
Chylothorax	6 (1.6)	1 (16.7)
Sepsis	5 (1.3)	4 (80.0)
Hoarseness	4 (1.0)	. . .
Pneumothorax	3 (0.8)	. . .
GI bleeding	1 (0.3)	. . .
Cardiovascular	2 (0.5)	2 (100.0)
Miscellaneous	4 (1.0)	. . .
Total	97 (25.3)	24 (6.5)

GI = gastrointestinal.

Among 267 patients who were discharged uneventfully from the hospital and regularly followed up, anastomotic stricture developed in 67, an incidence of 25.1%. Compared with the patients without anastomotic leakage, the interval of development of anastomotic stricture was significantly shorter for the patients with anastomotic leakage (with leakage, 76.0 ± 7.8 days, n = 12; without leakage, 135 ± 17.5 days, n = 55; $p < 0.01$). Furthermore, the incidence of anastomotic stricture was 37.5% (12/32 patients) after leakage but only 23.4% (55/235 patients) in patients without anastomotic leakage. All strictures were treated with esophageal dilation with satisfactory results. The average number of esophageal dilations was 3.9 per patient (range, 1 to 15). There was no local recurrence of carcinoma over the site of esophagogastrostomy.

Among 76 patients with more than 1-year survival who underwent functional evaluation of the gastric transplant, there were 18 patients undergoing pyloroplasty during use of the stomach as an esophageal substitute. The incidence of delayed functional disturbance and complications of gastric transplantation are shown in Table 4. The frequency of these delayed complications was as follows: acid or bile regurgitation, 35 patients (46.1%); postprandial fullness of abdomen, 29 patients (38.2%); dumping syndrome, 10 patients (13.2%); distended stomach with dyspnea, 9 patients (11.8%); aspiration pneumonia, 5 patients (6.6%); and gastric ulcer, 5 patients (6.6%). Moreover, compared with patients without pyloroplasty, those with pyloroplasty were found to have a higher incidence of development of bile regurgitation (55.5% versus 8.6%), dumping syndrome (33.3% versus 6.9%), aspiration pneumonia (16.7% versus 3.4%), and gastric ulcer (22.2% versus 1.7%).

Total esophageal substitute transit time was more than 72 seconds (n = 33) in the supine position, but only 16.6 ± 1.4 seconds during in the upright position. There was no statistical difference in esophageal transit times in the upright position between patients with and without pyloroplasty or pyloromyotomy (with pyloroplasty, 15.4 ± 2.6 seconds, n = 10; without pyloroplasty, 17.8 ± 1.8 seconds, n = 23; $p > 0.05$). In the ^{99m}Tc-HIDA test, all patients without pyloroplasty or pyloromyotomy except 2 (8.7%) had a normal secretion pattern, and no enterogastric bile reflux could be demonstrated. In contrast, 6 of 10 patients (60%) with pyloroplasty had evidence of enterogastric bile reflux in scanning.

Comment

From January 1959 to December 1984, a total of 1,808 patients with esophageal malignancies were admitted to the Division of Thoracic Surgery of Veterans General Hospital, Taipei. Before 1974, the colon was usually the esophageal substitute for our patients except in a few patients with lower esophageal carcinoma who underwent intrathoracic esophagogastrostomy. After 1974, this changed when a procedure to bring the stomach isoperistaltically through various routes to the neck as a transplant was established.

The stomach has a reliable and ample blood supply. It is well known that the stomach is large enough to reach the hypopharynx [15], except when the patient has had a subtotal gastrectomy or any other procedure where normal length of stomach is not available for esophagoplasty. Technically, esophagoplasty with the colon requires three anastomoses, whereas the isoperistaltic stomach is able to

Table 4. Incidence of Delayed Gastrointestinal Functional Disturbances and Complications of Using Stomach as Esophageal Substitute[a]

Group	Postprandial Fullness of Abdomen	Dumping Syndrome	Acid Regurgitation	Bile Regurgitation	Aspiration Pneumonia	Gastric Ulcer	Distended Stomach and Dyspnea	Total Patients
With pyloroplasty	7 (38.9)	6 (33.3)	8 (44.4)	10 (55.5)	3 (16.7)	4 (22.2)	3 (16.7)	18 (100)
Without pyloroplasty	22 (37.5)	4 (6.9)	24 (41.4)	5 (8.6)	2 (3.4)	1 (1.7)	6 (10.3)	58 (100)
Total	29 (38.2)	10 (13.2)	32 (42.1)	15 (19.7)	5 (6.6)	5 (6.6)	9 (11.8)	76 (100)

[a] Numbers in parentheses are percentages.

substitute for almost the entire esophagus with only one anastomosis. We agree with Akiyama's recommended principles for esophagoplasty with stomach: (1) orientation in a simple isoperistaltic fashion, (2) resection of the proximal half of lesser curvature and cardia of stomach, (3) effective preservation of the intraluminal vascular network, and (4) effective use of the size and stretchability of the stomach [5, 6, 8]. If the stomach is handled in keeping with these principles, success can be expected nearly every time.

Cervical esophagogastrostomy can be performed by bringing the stomach through retrosternal, posteromediastinal, and antesternal routes. Among these popular routes, the antesternal route is the longest and presents a cosmetic problem. The posteromediastinal route can be used only when the resection is complete, or early obstruction due to local recurrence of carcinoma or metastatic lymph nodes may occur. The retrosternal route is convenient and has been used predominantly (77.2%) among our patients.

Bilateral truncal vagotomies are inevitable during performance of esophagectomy for carcinoma of esophagus. Vagotomy can delay gastric emptying time [16]. From our studies, the emptying of the gastric transplant seemed to be under the influence of posture and gravity, and pyloroplasty failed to normalize the disturbed gastric emptying. The incidence of distended gastric transplant and epigastric fullness did not differ between patients with and without pyloroplasty in our series. Distended gastric transplant with full sensation may be partially caused by negative intrathoracic pressure, bilateral vagotomies, and traction tension over the gastric antrum and pylorus. This traction tension is probably due to angulation of the gastric transplant at the diaphragmatic margin, just beneath the xyphoid process of sternum, when the gastric transplant is pulled up through the retrosternal route. It is particularly obvious for patients with hepatomegaly. In addition, we recommend that the mediastinal pleura should be kept as intact as possible when the retrosternal tunnel is made. Intact mediastinal pleura is helpful to decrease the effect of negative intrathoracic pressure and prevent gastric transplant distention.

Although the gastric transplant was denervated, acid regurgitation still occurred rather frequently in our patients, which might be attributed to negative intrathoracic pressure and a distended gastric transplant. Acid regurgitation, however, was not difficult to treat with H_2 blocker. Furthermore, enterogastric bile reflux and dumping syndrome appear to occur more frequently in patients with pyloroplasty or pyloromyotomy, and these complications are rather hard to manage with medicine. Thus, similar to Collis [17], Shapiro and associates [18], and Angorn and colleagues [19], we firmly believe that a gastric drainage procedure is unnecessary with high esophagogastrostomy for reconstruction of the gastrointestinal continuity, except in patients with evidence of partial obstruction of pylorus. Most patients were able to eat a regular diet within 7 to 10 postoperative days. Body weight loss was frequently observed in the initial 3 to 6 months postoperatively, and then weight increased gradually. To prevent the occurrence of aspiration pneumonia, the patient should keep the upper chest and head elevated when lying down, particularly after meals.

Technical advances such as continual monitoring of central venous pressure, pulmonary wedge pressure, and arterial blood gas; preoperative and postoperative hyperalimentation; and perioperative respiratory therapy have progressively decreased the mortality rate of surgical management for carcinoma of esophagus. Our operative mortality rate for the entire series is 6.5%. Causes of death fall into three categories: pulmonary (66.7%), technical (25.0%), and cardiovascular (8.3%). Technical complications included anastomotic leakage, intraoperative or postoperative hemorrhage, and chylothorax. The recognized predisposing factors for pulmonary complications are old age, cigarette smoking, impaired pulmonary function, concomitant diseases (eg, diabetes mellitus, chronic obstructive pulmonary disease), poor nutrition, and prolonged duration of anesthesia [20]. Most of our patients were elderly and suffered from malnutrition before admission. Furthermore, history of cigarette smoking and evidence of obstructive pulmonary abnormalities were also rather frequent in our patients. Preoperative elimination of smoking, improvement of nutritional condition, postoperative prevention of pulmonary infection, and physiotherapy are very important to reduce the rate of pulmonary morbidity and mortality. Diminishment of wound pain by epidural anesthesia or analgesics is helpful for patient's deep breathing and effective cough. Bronchoscopic cleansing of bronchus is necessary if the patient is too weak to have effective expectoration. Pneumonia is better treated by a thorough bronchial cleansing than by antibiotics alone. In our series, 13 of 20 patients in whom pulmonary complications developed died.

Anastomotic leakage and pulmonary complications were the most common early complications in our series. It is possible that these two complications may be partly linked. An anastomotic leakage easily explains postoperative pulmonary complications, but postoperative hypoventilation of any origin may also influence the healing of the anastomosis.

Our anastomoses were performed manually in two layers using 3-0 Dexon or Vicryl, or in a single layer using 5-0 steel wire. We did not use autosuture for cervical esophagogastrostomy. Interrupted suture technique is our preference. Moreover, during the performance of esophagogastrostomy, we routinely cut the strap muscles of the neck and make an aperture behind the sternocleidomastoid joint about 4.0 to 5 cm in width. However, scanty oozing of dark blood at the site of anastomosis of the gastric fundus was still noticed rather frequently owing to mechanical obstruction at or distal to the suture line. In addition to mechanical obstruction inducing poor blood supply of the transplanted stomach, we believe that the etiology of anastomotic leakage may include: unrecognized and unrepaired mucosal defect at the time of anastomosis, uncontrolled infection adjacent to the esophagus, and overdistended transplanted stomach. The overdistended stomach may compromise respiration and also induce poor blood supply or edematous changes in the gastric transplant. Intact mediastinal pleura and adequate nasogastric tube decompression improve the distention of the gastric transplant immediately after operation. Our series had a slightly higher incidence (12.8%) of anastomotic leakage in comparison with others [2, 15, 21].

Anastomotic leakage is no longer a major complication of esophageal resection. Preoperative and postoperative total parenteral nutrition or the use of an alimentation jejunostomy has decreased the incidence of anastomotic leakage, morbidity, and mortality. Before feeding, we prefer to check for leakage by radiography or by having the patient drink diluted methylene blue dye (50 mL every 4 hours for 1 day) if the drainage tube is in position. Most of the cervical leakage can be sealed with proper conservative management, if not stressed by food ingestion. The incidence of leakage in our series was 13.2% for cervical anastomosis (41/310 patients) and 10.3% for intrathoracic anastomosis (6/58 patients). Only 3 of 47 patients (6.4%) in whom anastomotic leakage developed died postoperatively. Unfortunately, these 3 patients had leakage of the intrathoracic anastomosis. In other words, the mortality rate of leakage was 50% (3/6 patients) for intrathoracic anastomosis but 0% for cervical anastomosis. Therefore, leakage of a cervical esophagogastrectomy is not as grave as leakage of an intrathoracic esophagogastrostomy because it does not produce empyema and sepsis. Moreover, one can do fundoplication over the intrathoracic esophagogastrostomy, which may diminish the anastomotic leakage and prevent alkaline or acid reflux.

Four major causes of postoperative stricture of anastomosis have been considered: (1) leakage of anastomosis, (2) alkaline or acid reflux, (3) small circumference of anastomosis caused by technical error, and (4) local recurrence of carcinoma. Interestingly, none of our patients had local recurrence of carcinoma over the anastomotic site. In our series, the interval between operation and development of an anastomotic stricture was significantly shorter for the patients with anastomotic leakage as compared with those without anastomotic leakage ($p < 0.01$). If anastomotic stricture develops within 2 to 3 months, it is quite probably due to technical error or anastomotic leakage. In contrast, delayed stricture may be more frequently due to alkaline or acid reflux or local recurrence of carcinoma. Furthermore, the patients with anastomotic leakage had a higher incidence of development of anastomotic stricture than those without anastomotic leakage. Most postoperative stricture problems can be overcome with frequent esophageal dilations. None of our patients had complications develop during esophageal dilation. However, before esophageal dilation is performed or the diagnosis of stricture is made, all postoperatively dysphagic patients should have esophagoscopic examination. Any suspected lesion should undergo biopsy to prove or disprove anastomotic recurrence of carcinoma.

Delayed functional disturbance of the gastrointestinal tract or complications developed in more than half of our patients. These included postprandial fullness of abdomen, dumping syndrome, acid or bile regurgitation, aspiration pneumonitis, distended gastric transplant and dyspnea, gastritis, and ulceration of stomach. However, these delayed complications generally can be treated well with proper medication and physical therapy. Thus, most of the patients live well and regain their body weight. More than 80% of our patients can take care of themselves and their daily work, if there is no tumor recurrence or other associated diseases. Pyloroplasty does not improve these functional results.

Radical lymph node dissection was not routinely performed in the present series. Therefore, understaging of the postoperative histopathology in our series very possibly existed, particularly for the earlier stage cancers. The advanced cancers for most of our patients resulted in poor prognosis. The actuarial 5-year survival rate was only 7.6%, and the 2-year survival rate was 26.4% in our series.

We extend our deepest appreciation to Dr Ashis K. Mandle, Professor of Surgery-in-Residence, University of California, Los Angeles, for his suggestions and advice about this report during his 2-month visiting professorship at Veterans General Hospital, Taipei, Taiwan, ROC.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1994 may begin the recertification process in 1992. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1992. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Sclerosing Hemangioma of the Lung: Radiographic and Pathological Study

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The clinical, radiographic, and pathological features of 10 patients with sclerosing hemangioma of the lung seen between 1974 and 1990 were reviewed. The incidence of sclerosing hemangioma was 22.2% of benign tumors surgically resected during that time. There were 2 male and 8 female patients aged 15 to 77 years at operation, and 9 patients were asymptomatic. All 10 patients had a solitary tumor with a well-defined homogeneous round or oval shadow on chest roentgenograms. Chest computed tomography revealed a homogeneous soft-density mass in 4 patients and a low-density portion within the tumor because of a cystic change in 1 patient. Microscopically, 5 patients had a preponderantly solid pattern, 3 had a preponderantly papillary pattern, and 1 patient had a preponderantly sclerotic pattern. One patient had an equal mixture of solid and papillary patterns. Nine of the 10 tumors consisted of a mixture of at least three of the four major patterns. Regarding treatment, thoracotomy is indicated for a definite diagnosis. If a benign tumor is suspected at operation, an intraoperative frozen section is recommended. Once the diagnosis has been established as sclerosing hemangioma, a limited resection is indicated.

(Ann Thorac Surg 1992;53:295–300)

Sclerosing hemangioma, first described by Liebow and Hubbell [1] in 1956, is a rare benign lung tumor. It is characterized microscopically by four major histological patterns—solid, papillary, sclerotic, and hemangiomatous—in varying proportions. The histogenesis of the tumor is still unknown, although many investigators [2–8] have studied its origin using either an electron microscope or immunohistochemical methods. Clinically, the tumor shows a striking preponderance in middle-aged women, and in almost all patients with sclerosing hemangioma, the chest roentgenogram reveals a coin lesion that has a well-defined homogeneous margin and is considered to be benign. However, it is difficult to make a definite diagnosis preoperatively.

We present the radiographic features in relation to the pathological findings in 10 patients with surgically resected sclerosing hemangioma of the lung, emphasizing the diagnosis and treatment of the disease.

Material and Methods

During the period 1974 to 1990, 919 patients underwent surgical treatment of lung tumors at the Department of Surgery II, Faculty of Medicine, Kyushu University. Of these patients, 874 had malignant neoplasms (750 primary and 124 metastatic), and 45 had benign tumors or tumor-like lesions. There were 10 patients (22.2%) with sclerosing hemangioma among the 45 with benign tumors; the other 35 had hamartoma (n = 22), inflammatory pseudotumor (n = 9), and other benign tumors (n = 4). Their medical records and the findings of the radiological and histological examinations were also reviewed.

Results

Clinical Features

There were 2 male and 8 female patients with sclerosing hemangioma. They ranged from 15 to 77 years of age (average age, 42.0 years) at the time of operation, and more were in the fourth decade of life than any other. The clinical data are summarized in Table 1.

Of the 10 patients, 9 were asymptomatic. In 7 of these 9 patients, the tumor was discovered on routine chest roentgenograms and in 2, on chest roentgenograms during follow-up for other diseases. Only 1 patient had symptoms. This patient had been asymptomatic when the tumor was incidentally detected on chest roentgenogram. It was diagnosed as pulmonary tuberculosis and treated. The tumor had grown somewhat when a bout of cough and blood-tinged sputum occurred 12 years later. The period from detection of the tumor to operation ranged from 2 months to 12 years in these patients.

Radiographic Manifestations

All of the patients had a solitary tumor (Fig 1). It was located in the right upper lobe in 1 patient, the right middle lobe in 2 patients, the left upper lobe in 3 patients, and the left lower lobe in 4 patients. The greatest diameter of the tumor on the chest roentgenogram ranged from 13 to 82 mm; in 7 patients, it was less than 30 mm in diameter. The tumor doubling time in 2 representative patients was 660 days (patient 3) and 1,250 days (patient 7). The plain chest roentgenograms showed a well-

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Table 1. Clinical Data on Patients With Sclerosing Hemangioma of the Lung

Patient No.	Age (y)	Sex	Symptoms	Time from Detection to Operation	Location	Size[a] (mm)	Operation
1	54	F	None	3 mo	LLL (S9)	28 × 27	Lobectomy
2	38	F	None	1 y 3 mo	RML (S4)	40 × 35	Lobectomy
3	77	M	None	3 y 7 mo	LLL (S6)	82 × 77	Lobectomy
4	45	F	None	6 y 2 mo	RUL (S3)	23 × 23	Lobectomy
5	34	F	Cough, blood-tinged sputum	12 y	LUL (S3)	25 × 25	Enucleation
6	15	F	None	3 y	RML (S4)	23 × 20	Partial resection
7	31	M	None	7 y	LLL (S9)	36 × 28	Lobectomy
8	45	F	None	1 y 1 mo	LUL (S4)	13 × 12	Partial resection
9	30	F	None	3 y	LUL (S4)	24 × 21	Lobectomy
10	51	F	None	2 mo	LLL (S10)	18 × 18	Lobectomy

[a] This refers to the size of the tumor on plain chest roentgenogram.

LLL = left lower lobe; LUL = left upper lobe; RML = right middle lobe; RUL = right upper lobe; S = bronchial segment.

defined, homogeneous round or oval shadow in all patients.

Chest computed tomography was performed in 5 patients (patients 6 through 10) who had surgical resection after 1982 (Fig 2). Four had a homogeneous soft-density shadow with a smooth surface, and 1 showed a slightly irregular surface and a radiolucent portion within the tumor because of a cystic change, confirmed in the resected specimen.

Preoperative Diagnosis

In only 1 patient (patient 10) was sclerosing hemangioma suggested by a bronchoscopic brushing cytological examination, which revealed that the tumor cells had fine

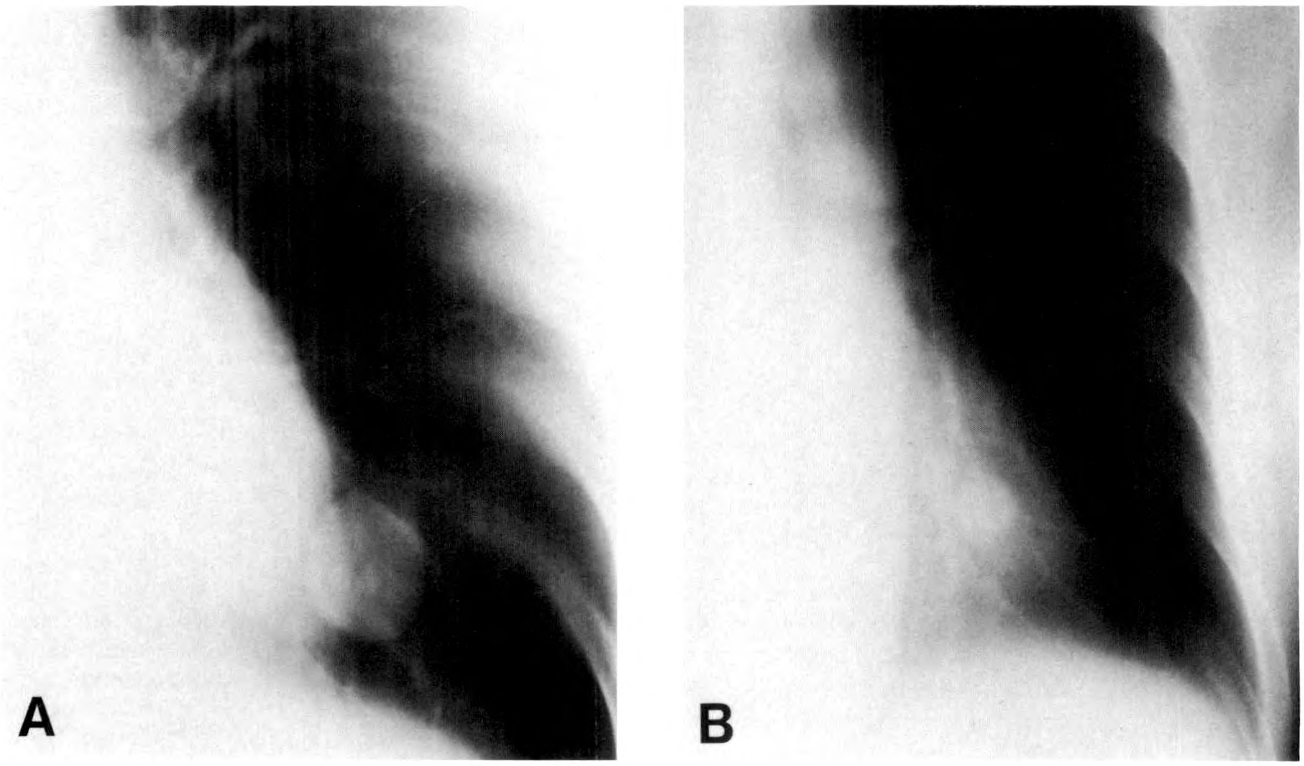

Fig 1. Tomogram of the left chest in (A) patient 7 and (B) patient 10 revealed a solitary homogeneous lesion with a well-defined margin.

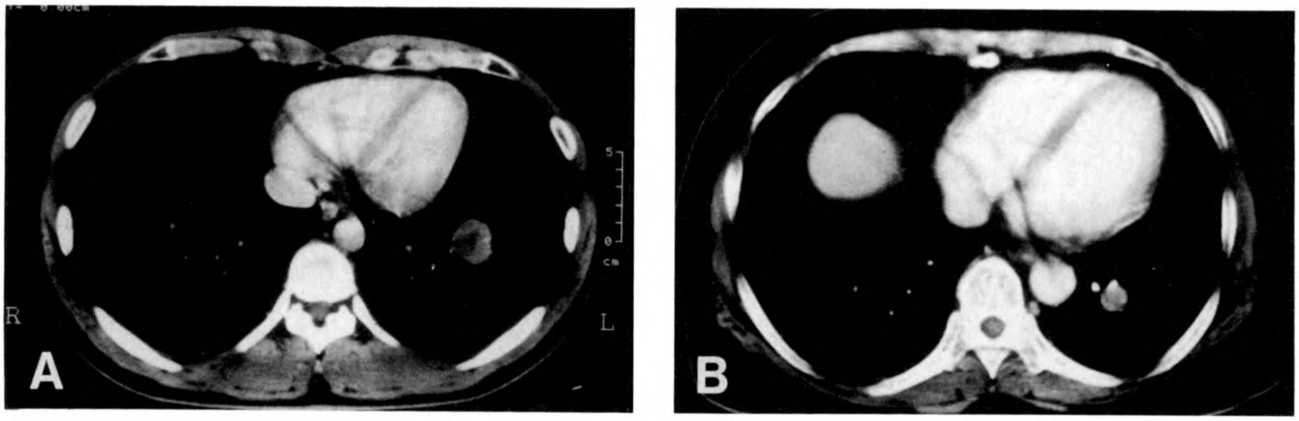

Fig 2. (A) (Patient 7.) Computed tomogram demonstrated a radiolucent lesion within the tumor, and an irregular margin was noted. (B) (Patient 10.) Computed tomogram revealed a homogeneous round mass adjacent to the artery.

granular hemosiderin in the cytoplasm and no atypical changes (Fig 3). Radiographic imaging indicated that nine tumors were benign.

Operative Findings

An intraoperative frozen section examination was performed on 3 patients (patients 6, 8, and 10) and led to a diagnosis of sclerosing hemangioma. An intraoperative cytological examination was performed on 3 patients (patients 5, 7, and 9). In 2 patients, no malignant cells were found, and in the other (patient 9), a carcinoid tumor was suspected.

A lobectomy was performed in 7 patients because the tumor was located near the hilar region in 6 and was a suspected carcinoid tumor in 1. A partial resection was performed in 2 patients and enucleation, in 1 patient. None of the 10 patients has experienced recurrence during follow-up ranging from 1 year to 16 years for the 7 patients treated by lobectomy and from 3 to 14 years for the 3 treated by limited resection.

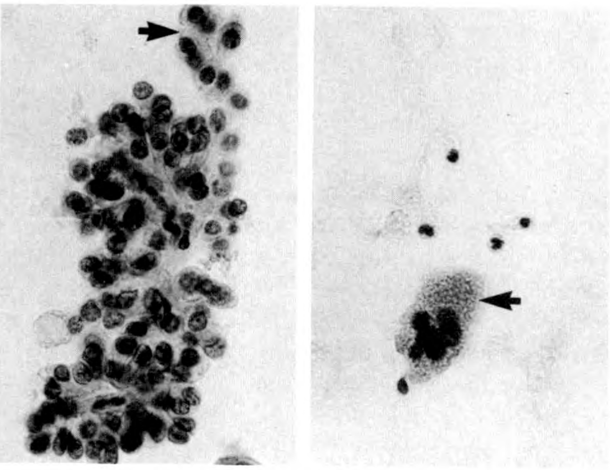

Fig 3. (Patient 10.) Bronchoscopic cytological examination showed no atypical changes and fine granular hemosiderin (arrow) *in the cytoplasm.*

Pathological Findings

Microscopically, the histological features of sclerosing hemangioma varied, and four major histological patterns were found in the same histological section: solid, papillary, hemangiomatous, and sclerotic patterns (Table 2). Five patients had a preponderantly solid pattern, characterized by large nests and sheets of round cells (Fig 4A), and 4 of the 5 had a marked hemangiomatous or hemorrhagic pattern (Fig 4B). Three patients had a preponderantly papillary pattern (Fig 4C), and 1 patient had a preponderantly sclerotic pattern, which was composed of loosely arranged spindle cells (Fig 4D). In only 1 patient was an equal mixture of solid and papillary patterns observed with sclerotic and hemorrhagic zones. Nine of the ten tumors contained a mixture of at least three of the four major patterns. Hemosiderin deposits were found in 6 patients, necrosis in 2, and a cystic change in 3.

Comment

Benign tumors of the lung are much less common than malignant tumors; their incidence ranges from 1% to 5% of lung tumors [9, 10]. Tengan and colleagues [10] reported that 15 of 48 benign tumors, excluding adenoma and inflammatory tumor, were sclerosing hemangiomas. The most common symptoms of patients with sclerosing hemangioma are cough, blood-tinged sputum, and chest pain, but 50% to 87% of patients in the literature [1–3, 11] were asymptomatic. Sclerosing hemangioma is noted to have some clinical characteristics, such as female preponderance and occurrence mostly in the fifth decade [2–4]. In the review of the clinical features of 196 patients with sclerosing hemangioma in Japanese patients by Kimura and associates [11], the average age was 46 years and the male to female ratio was 26:142. In our study, 80% of the patients were female, and 80% of the patients were in their fourth to sixth decade. The reason for the preponderance in women, however, remains unknown.

Katzenstein and co-workers [2] reported that the lesions were present on chest roentgenograms from 1 year to 14

Table 2. Pathological Findings in 10 Patients With Sclerosing Hemangioma of the Lung

Patient No.	Size[a] (mm)	Solid	Papillary	Sclerosis	Hemangiomatous	Hemosiderin	Necrosis	Cystic Change
1	20 × 20 × 20	Marked	Scanty	Moderate	Marked	+	–	–
2	30 × 25 × 25	Marked	Absent	Scanty	Marked	+	–	+
3	70 × 70 × 70	Scanty	Absent	Marked	Absent	–	+	–
4	30 × 20 × 20	Absent	Marked	Scanty	Scanty	+	–	–
5	25 × 20 × 20	Scanty	Marked	Moderate	Scanty	–	–	–
6	22 × 20 × 15	Marked	Absent	Marked	Marked	+	+	–
7	35 × 30 × 30	Absent	Marked	Moderate	Moderate	+	–	+
8	10 × 10 × 10	Marked	Absent	Scanty	Marked	–	–	–
9	20 × 20 × 20	Marked	Absent	Scanty	Moderate	–	–	+
10	12 × 9 × 9	Moderate	Moderate	Moderate	Moderate	+	–	–

[a] This is the size of the tumor in the resected specimen.

years before operation in 14 patients. In our study, the average age of the patients at the time of operation was 42.0 years, although the average age at first detection of the tumor was 38.6 years. Therefore, we assume that many patients with sclerosing hemangioma underwent various lengths of follow-up with periodic chest roentgenograms because the tumors were suggested radiographically to be benign or because the growth rate of the tumors was very slow. The tumor doubling time of sclerosing hemangioma in our representative patients was markedly longer than that of lung cancer, which has been reported to be about 5.5 months for adenocarcinoma and about 3 months for squamous cell carcinoma [12].

The greatest diameter of the lesion ranged from 0.4 to 8.0 cm in the reported cases, and about 90% of the lesions were less than 5.0 cm [13]. In our study, 70% of the lesions were less than 3.0 cm on chest roentgenograms. However, a smaller-sized tumor or a slow-growing tumor in itself does not exclude the possibility of malignant disease, as smaller-sized lung cancer tumors sometimes have no malignant findings radiographically. Toomes and colleagues [14] reported that a preoperative diagnosis of coin lesion of the lung, whether a benign or malignant tumor, could not be established in 32% of patients with a lesion smaller than 2 cm.

Radiographic features of sclerosing hemangioma usually include a well-defined, homogeneous round or oval shadow, which is quite different from that of malignant tumors. A lesion with an ill-defined margin, spicular radiation, pleural indentation, or vascular convergence is normally considered to be malignant. Such findings are usually never demonstrated in sclerosing hemangioma. Therefore, the feature of an irregular margin is very important in the differential diagnosis. However, in rare cases, pleural indentation [10] and spicular radiation [13] have been found. Sometimes a small radiolucent or radiopaque portion, which is due to a cystic formation or calcification, is observed in the tumor and is clearly demonstrated on the chest computed tomogram. We found three instances of cystic formation, but no instance of calcification was observed. Katzenstein and associates [2] reported that 41% of sclerosing hemangiomas had calcification. In general, evidence of calcification in a tumor is a radiological assurance that it is benign.

Bronchial arteriography is sometimes useful for diagnosing sclerosing hemangioma [10] by demonstrating a characteristic vascular network wrapped around the tumor. The surface of the tumor is hypervascular, but no definite tumor stain within the lesion is noted. Bronchoscopic cytological and pathological examinations are useful for malignant neoplasms. For benign tumors, however, great caution is needed to make a definite diagnosis when only these methods are used, because the absence of malignant cells does not always exclude malignant disease.

Liebow and Hubbell [1], the first to describe sclerosing hemangioma, suggested this tumor was an endothelial proliferation, and some investigators [15,16] confirmed an endothelial origin by electron microscopic studies. Other studies have shown evidence of a mesothelial origin [17]. However, based on ultrastructural studies and recent immunohistochemical analysis, some investigators [3–8, 18] now consider this tumor to be primarily a proliferation of epithelial cells. The results of positive staining for epithelial membrane antigen and surfactant apoprotein, which are the markers of epithelial cells [4, 6, 7], and the results of negative staining for factor VIII–related antigens for endothelial cells [6, 8] suggest that the origin of sclerosing hemangioma might be type II pneumocytes. In spite of these studies, the exact histogenesis of sclerosing hemangioma remains uncertain.

Sclerosing hemangioma should be recognized as a distinct clinicopathological entity. We need to consider sclerosing hemangioma as one of the differential diagnoses, especially when the patient is female and a relatively young adult with a well-defined, homogeneous round shadow on the chest roentgenogram. Thoracotomy

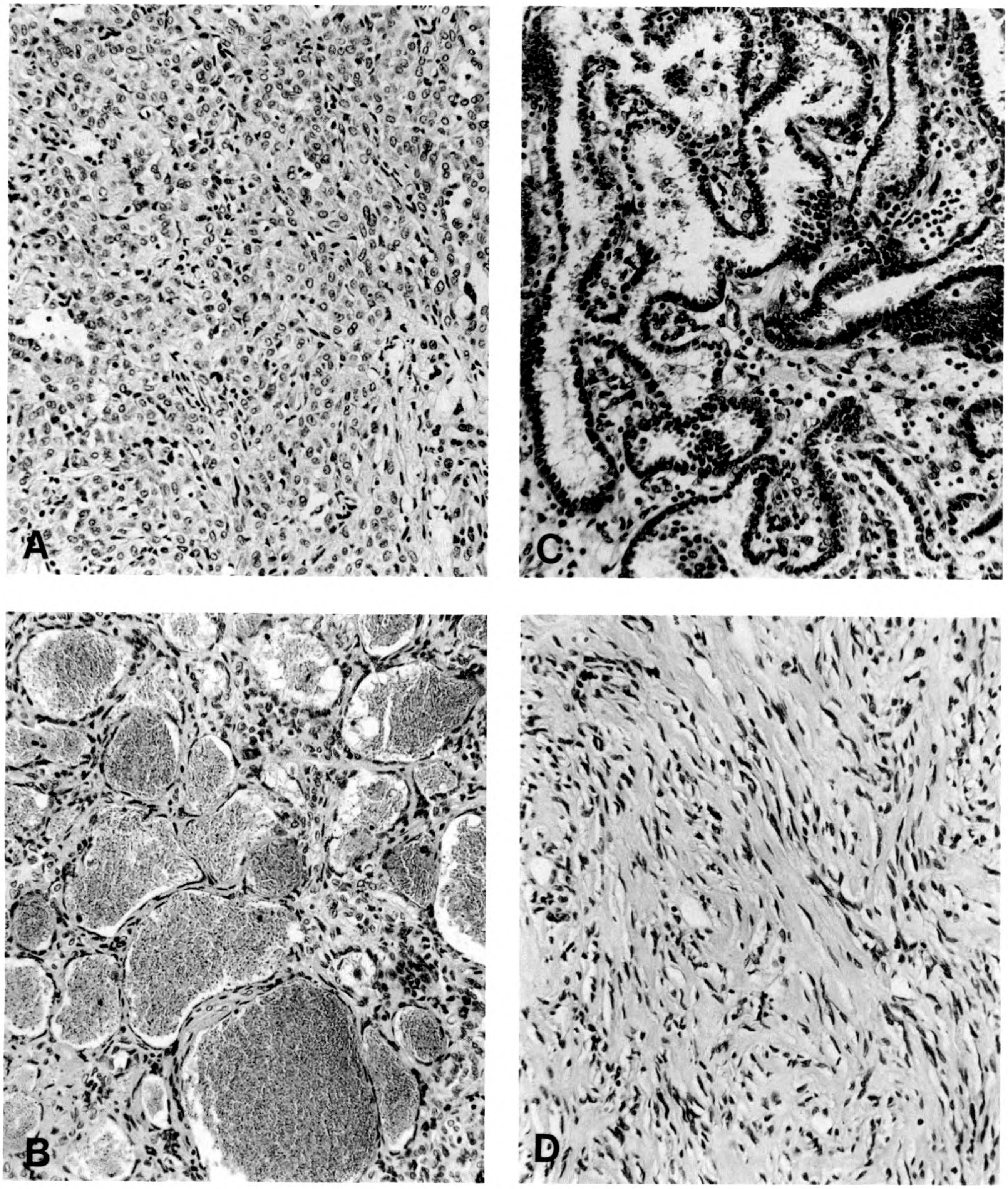

Fig. 4. Four major histological features in sclerosing hemangioma: (A) solid cellular pattern (patient 10), (B) hemangiomatous pattern (patient 8), (C) papillary pattern (patient 7); and (D) sclerotic pattern (patient 3). (Hematoxylin and eosin; ×210 before 3% reduction.)

is indicated for a definite diagnosis because it is difficult to make a definite diagnosis preoperatively. If a benign tumor is suspected at operation, an intraoperative frozen section is recommended. Once sclerosing hemangioma has been diagnosed, complete removal of the tumor by limited resection, if possible, should be performed.

We thank Dr Brian T. Quinn for critical comments.

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INVITED COMMENTARY

Pulmonary sclerosing hemangioma is an enigmatic neoplasm that has a characteristic clinical presentation as reflected in this report by Sugio and associates. The tumor typically is seen in middle-aged asymptomatic women as a solitary peripheral, well-circumscribed nodule, which may be partially calcified. By gross examination it is frequently hemorrhagic, and this observation led to the hypothesis by Leibow and Hubbell that these tumors were endothelial-derived.

The evolution of our understanding since its description has been both clinical and pathogenetic. We now recognize that pulmonary sclerosing hemangioma may be seen as solitary or multiple nodules, that there may be malignant variants, and that the right middle lobe is not the sole site of occurrence. Immunohistochemical studies have also led to new conclusions: the proliferative cell is probably not a mesenchymal cell, but rather a primitive respiratory epithelial cell showing cellular differentiation akin to the cells of the peripheral airways and alveolar septa. This is suggested by the expression of cytokeratin filaments, epithelial membrane antigen, and surfactant apoprotein. Consequently, pulmonary sclerosing hemangioma is currently believed to represent an epithelial proliferation—an alveolar pneumocytoma—that is usually clinically benign and surgically curative.

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Effects of Shaving Methods and Intraoperative Irrigation on Suppurative Mediastinitis After Bypass Operations

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To investigate the effects of the hair removal methods and intraoperative irrigation on suppurative mediastinitis after cardiopulmonary bypass operations, 1,980 consecutive adult patients over a 2-year period in our institution were prospectively randomized to manual shaving versus electrical clipping of hair before the skin incision, and to povidone-iodine solution (0.5%) versus saline solution mediastinal and subcutaneous irrigation before wound closure. The overall incidence of suppurative mediastinitis was 0.86% (17/1,980). The infectious rate was significantly higher in the manually shaven (13/990) than in the electrically clipped patients (4/990) with an odds ratio of 3.25 (95% confidence interval, 1.11 to 9.32; $p = 0.024$). It was also higher in the povidone-iodine group (11/990) than in the saline group (6/990), although the difference was not statistically significant ($p = 0.16$). Fourteen patients were treated with operative debridement with closed tube irrigation, with one failure requiring a conversion to an open wound. Two patients were successfully treated with primary open wound procedures followed by delayed muscular flap closures, and 1 patient succumbed to rapid and profound sepsis soon after open drainage. We conclude that electrical clipping is superior to manual shaving in the prevention of suppurative mediastinitis. The routine use of povidone-iodine (0.5%) irrigation was of no benefit in this study and may increase the incidence of infection due to its known suppressive effects on local leukocytes and fibroblasts. Furthermore, operative debridement with closed tube irrigation was successful in treating the majority of cases in this series.

(Ann Thorac Surg 1992;53:301–5)

Since the collective review by Sarr and his associates [1] on deep sternal wound infection after cardiopulmonary bypass operations, more recent studies have reported incidences of this complication in the range of 0.97% to 2.1% with associated mortalities of 14% to 39.6% [2–6]. Although this complication is infrequent, when it occurs it poses a threat to the integrity of the adjacent vascular structures. It is a potential source of bacterial seeding of prosthetic valves and conduits, and of eventual sepsis. Continuing efforts are needed to minimize this dreadful complication. The traditional efforts used in our institution to prevent this complication include skin shaving, chlorhexidine shower, preoperative skin preparation with alcohol and povidone-iodine scrubs, painting with tincture of iodine, prophylactic antibiotics, and mediastinal plus subcutaneous irrigation before wound closure.

The current study was designed to investigate prospectively two variables that can be controlled by the surgeons. Violation of the skin barrier by shaving with a razor has been implicated as a cause of bacterial wound contamination and has been associated with increased wound infection in elective general surgical operations [7, 8]. The authors of these studies and others have advocated abandoning preoperative shaving or replacing it with clipping of hair [9, 10].

Mechanical debridement by fluid irrigation of wounds is fundamental in the deterrence of bacterial infection. Irrigation with povidone-iodine solution has been shown by our institution to be effective as a part of the management of sternotomy wounds with established bacterial infection [6]. We hypothesized that the routine use of a povidone-iodine solution as an intraoperative irrigant may reduce the local bacterial counts and, therefore, may reduce the overall wound infectious rate. However, povidone-iodine has known local inhibitory effects on leukocytes and wound fibroblasts in addition to its antibacterial effects [11]. Therefore, the routine use of povidone-iodine irrigation before wound closure has both advantages and disadvantages that may affect the overall infectious rate, and this formed the basis of this study.

The relative consistency in the creation and closure of the sternotomy incision makes this population of surgical patients ideal candidates for this type of investigation. This prospective, randomized study involving 1,980 consecutive adult patients who underwent cardiopulmonary bypass operations through the sternotomy incision over a 2-year period in our institution was designed to delineate the effects of razor shaving versus electrical clipping and saline versus povidone-iodine irrigations on the development of suppurative mediastinitis.

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Patients and Methods

From July 1987 to June 1989, 1,980 consecutive adult patients were randomized into manual shaving with a razor versus electrical clipping (Remington, 3M), and saline (0.9% NaCl) versus povidone-iodine (0.5% in NaCl solution) intraoperative irrigation according to the last two digits of their hospital numbers. The actual choices of shaving and irrigants were recorded at the time of the procedures and blinded from the attending surgeons. The records of randomization and the charts of the infected patients were reviewed at the end of the study period.

The study included elective and emergent cases. Shaving was performed on the night before the elective operations, and on the operating table for the emergency cases. All patients received perioperative antibiotics with the first dose given on the way to the operating room, and antibiotic administration was continued for at least 24 hours. Cefazolin was used for the uncomplicated cases, and it was replaced by vancomycin for the penicillin-allergic patients. All patients except the few who required closed chest compression before the skin incision received at least 10 minutes of thorough alcohol and povidone-iodine scrubs. The skin was then dabbed dry and painted with tincture of iodine (1%). The perineum was isolated by cotton towels. The borders of the operative sites were draped by adhesive paper towels, then overlayed by adhesive transparencies (3M). The mediastinum was irrigated with 1 to 3 L of the chosen irrigant right before sternal closure, which was performed by stainless steel wires through the sternum. Absorbable oxidized cellulose rather than bone wax was used to control venous oozing from the sternal edges. The edges of the pectoralis major muscular fascia were tightly reapproximated by two running Vicryl stitches (Ethicon, Somerville, NJ). The subcutaneous wound was copiously irrigated before the skin was closed with stainless steel staples. Mediastinal and pleural chest tubes were usually removed within 24 hours postoperatively.

Wounds were examined by the surgical team at least twice a day. Symptoms and signs of deep sternal wound infection that were sought included unusual sternal pain, fever, wound erythema, drainage, warmth, sternal instability and tenderness on palpation, and leukocytosis. Needle mediastinal aspiration was occasionally (2 patients) needed to aid in making the diagnosis. Computed tomographic scanning was used only in 1 patient. Sterile sternal bone dehiscence and subcutaneous wound infection and problems were not included in this group of patients with suppurative mediastinitis.

All infected patients were treated surgically. The sternal wound was reopened in the operating room under general anesthesia. All sternal wires were removed; necrotic and grossly infected tissues were debrided. The skin and subcutaneous tissue was usually cut back several millimeters. The edges of the sternum were debrided by a rongeur. Multiple specimens were obtained for bacterial culture and sensitivity analysis. The mediastinum was then irrigated with a copious amount of a povidone-iodine solution (0.5%). The choice between a closed wound with tube irrigation and an open packed wound with the intent of subsequent muscular flap delayed closure was then made by the operating surgeon based on the severity of the infectious process as evidenced by the appearance of the wound at the time of the operation. These two methods have been described in detail previously [5, 12]. Tube irrigation for the closed wounds was continued for 7 to 10 days; the irrigants included povidone-iodine solution and various antibiotic solutions chosen specifically for the isolated organisms. The choices of intravenous antibiotics were adjusted based on the sensitivities of the isolated organisms; repeated cultures of the irrigating fluid were obtained to detect the development of drug resistance. The intravenous antibiotics were continued until the irrigation tubes were removed and all the signs of infection had been eradicated. All patients were continued on a prolonged course of oral antibiotic at the time of discharge.

Statistical analysis was performed by Fisher's exact test; risk ratio and 95% confidence limit were calculated by Mantel-Haenszel statistics. Values are reported as means ± standard deviations when appropriate.

Results

During the 2-year study period, 1,980 consecutive adult patients having cardiopulmonary bypass and a sternotomy incision were included in the randomization. The operations included coronary artery bypass graftings, valvular replacements, combinations of coronary artery bypass grafting and valvular replacement, repairs of thoracic aneurysms, and resections of cardiac tumors (Table 1). There was no incidence of deep sternal wound infection among the latter two types of operations. The incidences of infection were similar in the coronary artery bypass grafting, valvular replacement, and coronary artery bypass grafting plus valvular replacement groups.

The onset of deep sternal wound infection ranged from 4 to 30 days postoperatively, with an average of 10.6 days. The diagnosis was made in all but 2 patients before they were discharged from the hospital after their original operations. The usual signs of infection were not reliably present in this series of patients (Table 2), with purulent drainage being the most prevalent and sternal tenderness being the least common. Of note is that slightly more than half of the patients did not have fever or leukocytosis at the time of diagnosis. The average temperature was 38.2°C (range, 37.4° to 39.4°C), and the average white blood cell count was 13 × 10^4/L (range, 7.9 to 27.9 × 10^4/L). Sternal dehiscence was detected preoperatively in close to half of the patients. Skin organisms were commonly the causative agents as listed (Table 3). The 2 patients with polymicrobial infection had infection that involved gram-negative organisms.

Superficial wound cellulitis that only required treatment with antibiotics, subcutaneous wound infection and problems, and sterile sternal bone dehiscence due to faulty sternal wire placement were not included in the consideration of the complication (suppurative mediastinitis) in question. There were 5 patients with subcutaneous wound infection and 4 patients with chronic wound draining sinus tracts. These patients presented with their

Table 1. Incidence of Sternal Wound Infection, Treatments, and Mortality by the Types of Operation

			Treatments		
Operation	No. of Patients	Infection (%)	Closed[a]	Open[b]	Mortality
CABG	1,497	12 (0.80)	11	1	1
VR	150	3 (2.0)	2[c]	1	0
VR + CABG	144	2 (1.39)	1	1	0
Other	188	0	0	0	0
Total	1,980	17 (0.86)	14	3	1

[a] Debridement, reclosure of sternal wound with tube irrigation. [b] Debridement, open and packed wound with delayed muscular flap closure. [c] One failure converted into an open wound.

CABG = coronary artery bypass grafting; VR = valvular replacement.

problems at a median of the 42th postoperative day (range, 24th day to sixth year). These patients were successfully treated by local operative debridement and occasional removal of the sternal wires involved; none of these patients required mediastinal reexploration. There were 8 patients in whom sterile sternal bone dehiscence developed that required complete rewiring at a median of the 15th postoperative day (range, 7th to 84th day); half of these patients presented with this problem after being discharged from their original hospitalizations. These patients received prophylactic antibiotics for the rewiring procedure and were deemed not to have deep sternal wound infection based on operative findings and intraoperative cultures.

There were a total of 17 patients who were found to have the clinical and operative findings of suppurative mediastinitis, an incidence of 0.86% or 17/1,980. As stated in Table 4, the infectious rate was significantly higher in the razor-shaven group than in the electrically clipped group with an odds ratio of 3.25 (95% confidence interval, 1.11 to 9.32; $p = 0.024$). This was also nearly twofold higher in the povidone-iodine group than in the saline group, although the difference was not statistically significant. Logistic regression analysis did not reveal interaction between the two randomized variables.

In this series, emergency operations and reoperations for excessive postoperative bleeding were not associated with significant increases in the incidence of suppurative mediastinitis ($p > 0.05$; see Table 4). Interestingly, the infectious rate was lower among patients who had unilateral or bilateral internal mammary arterial conduits than in patients who had only saphenous aortocoronary bypass grafts. The cardiopulmonary bypass time and aortic cross-clamp time were similar between the noninfected and infected patients. The pump times for the noninfected and infected patients were 101 ± 50 and 103 ± 6 minutes, respectively. The aortic cross-clamp times for the noninfected and infected patients were 55 ± 28 and 56 ± 5 minutes, respectively.

Table 2. Clinical Findings of Sternal Wound Infection

Sign/Symptom	No. of Patients (%) (n = 17)
Purulent drainage	12 (71)
Sternal instability	8 (47)
Leukocytosis	8 (47)
Fever (>38°C)	7 (41)
Atypical pain	5 (29)
Erythema	4 (24)
Sternal tenderness	2 (12)

Fourteen patients were treated with operative debridement with closed wound and tube irrigation, with only one failure requiring a conversion to an open wound. The sternal wound infection of this particular patient was diagnosed during her follow-up office visit 30 days after her original aortic valve replacement. The infection was under control after the wound was left open, and the wound was subsequently closed by a muscular flap procedure. Two patients were treated with debridement and open wound; both tolerated delayed muscular flap closures. The last patient was in profound sepsis at the time of the diagnosis of his sternal wound infection, which was made 21 days after his coronary artery bypass grafting. He died soon after opened drainage, constituting the only mortality in this series of sternal wound complications.

Comment

The commercially available povidone-iodine solution (Betadine; Purdue Frederick, Norwalk, CT) contains a compound consisting of molecular iodine complexed with a polymer, polyvinylpyrrolidone in water. The bactericidal effects of povidone-iodine are due to the direct effects of free iodine in solution. Iodination of membrane and

Table 3. Microbial Organisms

Organism	No. of Patients[a]
Gram-positive (10 patients)	
Staphylococcus epidermidis	5
Staphylococcus aureus	4
Propionibacterium	1
Gram-negative (5 patients)	
Enterobacter aerogenes	2
Klebsiella oxytoca	2
Serratia marcescens	2
Enterobacter atriogena	1
Enterobacter cloacae	1

[a] Two patients had two or more organisms isolated.

Table 4. Risk Factors for Sternal Wound Infection

Factor	Incidence (%)	*p* Value
Shaving	13/990 (1.3)	0.02
Clipping	6/990 (0.6)	
Povidone-iodine irrigation	11/990 (1.1)	0.16
Saline irrigation	6/990 (0.6)	
IMA conduit	5/808 (0.6)	0.07
SVG conduit	12/815 (1.5)	
Elective	13/1761 (0.7)	0.11
Emergency	4/219 (1.8)	
Reop for bleeding	1/79 (1.3)	0.49
No reop for bleeding	16/1901 (0.8)	

IMA = internal mammary artery; reop = reoperation; SVG = saphenous vein graft.

cytoplasmic proteins leads to rapid killing of bacteria. Polyvinylpyrrolidone does not have any intrinsic antibacterial activity. However, its affinity for the cellular membrane greatly enhances iodine's bactericidal activity by delivering it to the cell surface. The amounts of free iodine and complexed iodine in povidone-iodine solution remain in a dynamic equilibrium, and the relative amounts depend on the concentration of the solution, the majority of iodine being in the complexed form. The maximum amount of free iodine has been determined to exist in 0.7% solution [13]. Povidone-iodine in 5% solution has been shown to reduce human leukocyte chemotaxis and fibroblastic activity in healing wounds, but these deleterious effects were not detected in 1% solution [14]. The characteristics and clinical relevance of povidone-iodine solution were well described by Zamora [11]. With these issues in mind, a 0.5% povidone-iodine solution was used in this study.

The use of povidone-iodine solution in continuous tube irrigation after operative debridement and reclosure of the wound has been demonstrated to be an effective treatment for sternal wound infection [6]. The efficacy of povidone-iodine solution as a routine intraoperative irrigant to prevent sternal wound infection is unclear. There are numerous sources of bacterial wound contamination during cardiopulmonary bypass operations that are difficult to avoid [1]. This study was designed with the hypothesis that rigorous intraoperative mediastinal and subcutaneous irrigation with a diluted povidone-iodine solution may better prevent the complication of deep sternal wound infection than the traditional use of saline solution. On the contrary, the data revealed a higher incidence of sternal wound infection in the povidone-iodine group. Although the difference was not statistically significant, one may conclude that povidone-iodine solution when used in the concentration in this study was of no benefit in the prevention of suppurative mediastinitis. In the absence of active infection, this study suggests that the deleterious effects of povidone-iodine on the fibroblast and leukocyte activities in a fresh surgical wound outweigh its antibacterial effects, and this may even lead to a higher incidence of wound infection.

Early description of operative procedures noted the importance of hair removal to improve exposure and wound aesthetics and to avoid entanglement with skin sutures. In the development of surgical asepsis and antisepsis in the beginning of the 20th century, hair has been regarded as a carrier of pathogens and is to be removed at the operative sites. This tradition has been an important part of preoperative management to the present day. More recently, the question of whether different methods of shaving have an effect on wound infection rates has been addressed. Manual skin shaving with a razor has been shown to cause microscopic breakage in the epithelial barrier, leading to bacterial contamination of the surgical wound. This effect worsens with increasing delay between the time of shaving and the operation [8]. Shaving with an electrical clipper was associated with a lower incidence of wound infection than razor shaving in general surgical wounds [7]. The result of the current study on the sternotomy wound is in agreement with the study on other types of wounds, and supports the current understanding of the pathogenesis of surgical wound infection.

Although we believe that early postoperative sternal bone dehiscence may be a risk factor for the development of deep sternal wound infection, we have no data of our own nor have we found any data in the literature to support this possibility. Therefore, isolated sternal table instability, when detected clinically in the absence of any signs of infection, does not necessitate operative rewiring in our practice unless there are other indications such as respiratory compromise or excessive pain. The patients who required rewiring for sterile sternal bone dehiscence were not included in the infected group. We emphasize that this study excluded the patients with superficial wound problems.

Risk factors for deep sternal wound infection after cardiopulmonary bypass operations have been extensively reported. Although the identification of risk factors was not an emphasis of the present study, several important associated factors need to be addressed for comparison with other studies. Numerous published series reported that emergency operations and reoperation for bleeding were associated with significantly increased risks of sternal wound infection after cardiopulmonary bypass operations [1, 4, 5, 12]. We also found a 2½-fold increase in the infectious rate of the emergency operations as compared with the elective cases ($p = 0.11$). The finding of this study, however, could not support that reoperation for postoperative bleeding was a risk factor for sternal wound infection in this institution.

Several studies have reported an association between the use of the internal mammary artery for aortocoronary bypass and sternal wound infection. Although some demonstrated an association with only the use of bilateral internal mammary arteries [2, 15], others have reported an association with single or double internal mammary arteries [5, 16]. This risk factor is attributed to devascularization of the sternum from the dissection of the internal mammary artery off the chest wall, and this theory was substantiated by a cadaveric study on the vascular supply of the human sternum [17]. On the contrary, the patients who received internal mammary arterial conduits in this series had a 2½-fold lower infectious rate than the patients who received saphenous vein bypass grafts ($p = 0.07$). This can be explained by the patient selection for the use of internal mammary artery conduit in our institution, where old age, emergency operation, hemodynamic instability, obesity, and chronic obstructive pulmonary disease are considered to be relative contraindications. Therefore, the patients with increased risks for sternal wound infection were preselected to be in the saphenous vein bypass graft group. This type of preselection warrants caution in interpreting results from other retrospective, nonrandomized studies on this issue.

Culliford and co-workers [12] have outlined the surgical approach in treating deep sternal wound infection, with the options of the closed method (debridement, reclosure, and continuous tube irrigation) and the open method (debridement, packed open wound, and delayed secondary closure). The closed method was successful in treating 90% of the early sternal infections (diagnosed less than 30 days after the original operations) in their series of patients. The current study reaffirms that the majority of cases can be treated successfully with the closed method in this series of patients who were all diagnosed within 30 days of the operations (average, 10.6 days). This finding contests the recommendation of several studies advocating the use of a muscular flap procedure as a primary or one-stage operative treatment to manage this problem [18–21]. We did not study or compare our approach with the primary muscular flap procedure, as we used the muscular flap transposition only as a method of delayed wound closure after primary open debridement in the severe cases of infection. Nevertheless, it appears logical that a lesser operation such as debridement/closed tube irrigation is preferable to an extensive reconstructive procedure if they are equally effective, despite the lack of a randomized, prospective study.

In summary, this prospective, randomized study demonstrated that electrical clipping is superior to razor shaving and that intraoperative irrigation with povidone-iodine in 0.5% solution was of no additional benefit over simple saline irrigation in the prevention of deep sternal wound infection after cardiopulmonary operations. The low overall infectious rate can be attributed to the administration of prophylactic antibiotics as well as the use of rigorous mediastinal and subcutaneous wound irrigation before wound closure. In this series, the success of the closed technique as a primary treatment and the overall low mortality rate of the infected patients were likely due to early detection of this infectious complication.

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Heart, Heart-Lung, and Lung Transplantation in the First Year of Life

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Seventeen infants less than 1 year of age have undergone heart (12), heart-lung (3), and lung (2) transplantation for end-stage cardiopulmonary disease. The infants undergoing heart transplantation had a mean age of 4.5 months (range, 19 days to 12 months) with the diagnosis of cardiomyopathy in 4 and congenital heart disease in 8. Four of the 8 patients (50%) had hypoplastic left heart syndrome. Actuarial survival at 1 and 2 years was 74% and compared favorably with the survival of older children at 1 and 2 years of 82% and 69%. The linearized rejection rate was less in infants as compared with children more than 1 year of age (0.61 versus 1.48 episodes per 100 patient days). In intermediate follow-up, no graft atherosclerosis has been noted. Immunosuppression has included a three-drug protocol of cyclosporine, azathioprine, and prednisone. A steroid taper to alternate day steroids or off completely by 6 months has been the goal and has been accomplished in 6 of 12 infants. Heart-lung and lung transplantation has been performed in 5 infants. One infant in each group died: 1 infant secondary to airway complications and sepsis and another due to pulmonary sepsis. A pulmonary lobe from a larger and older donor was transplanted into a 4-week-old infant as a single-lung transplant with good outcome. The 3 surviving infants are well 24, 18, and 2 months after transplantation. Obliterative bronchiolitis has not been clinically apparent in this group. These data support the clinical efficacy of heart, heart-lung, and lung transplantation in the first year of life.

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Heart transplantation has been performed in an increasing number of pediatric patients over the past 5 years. In 1990, an estimated 8% to 10% of the total number of heart transplantations were performed in the pediatric age group. With a growing experience in pediatric heart transplantation, patients have become younger and the indications for heart transplantation more diverse [1–3]. Bailey and associates [4, 5] ushered in a new approach to therapy for infants with severe congenital malformations of the heart when they performed the first heart transplantation for hypoplastic left heart syndrome (HLHS). For the first time, palliative operations were being compared with heart transplantation with respect to survival and long-term outcome [6]. Therefore, heart transplantation has become part of the armamentarium of the physician dealing with infants and children with end-stage heart disease either from severe congenital malformations or cardiomyopathies. In 1986, the Stanford cardiac transplant program began accepting infants for heart transplantation and shortly thereafter began accepting infants with combined cardiopulmonary diseases for heart-lung and lung transplantation. In this report, a summary of this experience will be given, in addition to comparisons made with the older children (1 to 14 years) with respect to survival, rejection, infection frequency, and graft atherosclerosis.

Patients and Methods

From December 1986 through December 1990, 12 infants underwent heart transplantation at an average age of 4.5 months (range, 19 days to 12 months). There were 5 male and 7 female patients. The preoperative diagnoses were cardiomyopathy in 4 and congenital heart disease in 8. Four of the 8 had the diagnosis of HLHS. The average follow-up was 1.5 years, and the cumulative follow-up was 16.9 patient years. Five infants underwent either heart-lung or lung transplantation. There were 4 male patients and 1 female patient, and the range of follow-up was 1 month to 2 years.

Three of 5 infants underwent heart-lung transplantation at ages 4, 10, and 12 months for end-stage cardiopulmonary disease. Single lung transplantation was performed in 2 infants at ages 1 month and 12 months for severe primary pulmonary hypertension and bronchopulmonary dysplasia.

Recipient and Donor Selection

Infants evaluated for transplantation had either intractable heart failure or a severe congenital cardiac malformation. Four infants had cardiomyopathies with shortening fractions less than 0.15 and congestive heart failure unre-

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sponsive to medical therapy. Four infants with HLHS received allografts; however, an additional 6 infants listed for cardiac transplantation did not receive allografts owing to the unavailability of suitable donors. These 6 infants were successfully palliated with the first-stage Norwood procedure. Four infants had severe left ventricular function secondary to an anomalous left coronary artery and underwent cardiac transplantation.

Three infants underwent heart-lung transplantation for pulmonary atresia and single ventricle, HLHS with pulmonary hypertension, and pulmonary venous stenosis after attempted repair. Two infants received single lung transplants at 1 month and 12 months for severe pulmonary hypertension and bronchopulmonary dysplasia. The infant with severe pulmonary hypertension received a pulmonary allograft after 4 weeks of extracorporeal membrane oxygenation support. This allograft was the left upper lobe of a 2-year-old child weighing 15 kg as compared with the recipient weight of 3.0 kg. Pulmonary transplantation in this infant was made possible by applying the principle of lobar transplantation; otherwise, no suitable donors would have been available.

Donors were selected according to ABO blood group, size, and absence of cardiac dysfunction. Lung donors had to have a clear chest roentgenogram, satisfactory arterial blood gases (oxygen tension greater than 100 mm Hg on an inspired oxygen fraction of 0.4), no evidence of infection in endotracheal aspirate, and normal pulmonary mechanics. The cardiac allografts were harvested with standard techniques using crystalloid cardioplegia, with an average ischemic time of 187 minutes and a range of 95 to 495 minutes. The heart-lung blocks were taken using the same crystalloid cardioplegia and a modified Euro-Collins solution for pulmonoplegia. Pulmonoplegia was administered after pretreatment of the donor with prostaglandin E_1 at a dose of 125 ng/kg/min over 5 to 6 minutes. The volume of pulmonoplegia infused was 60 to 90 mL/kg of body weight. The longest ischemia time on a heart-lung block has been 240 minutes with good graft function.

Most infant donors were resuscitated victims of child abuse and sudden infant death syndrome. Cardiac resuscitation in the donor did not preclude successful transplantation if careful evaluation was performed. To determine the adequacy of a particular donor, echocardiography was performed and the amount of inotropic support noted.

Immunosuppression

A three-drug protocol of cyclosporine, azathioprine, and prednisone was used. Preoperative cyclosporine and azathioprine were given if the heart transplantation did not involve circulatory arrest as part of the transplant procedure. Intraoperatively, methylprednisolone (10 mg/kg) was given at the termination of cardiopulmonary bypass. In the postoperative period, intravenous cyclosporine administration was common for 3 to 4 days after transplantation. This was usually given at a dose of 0.1 to 0.2 mg/kg/day to achieve serum levels of 150 to 250 ng/mL by radioimmunoassay. After this initial period, cyclosporine was given three times per day for an average dose of 12 mg/kg/day (Table 1). Azathioprine was given to leukocyte tolerance (white blood cell count greater than 4×10^6/L). Prednisone was given in a tapering dose beginning at 0.6 mg/kg/day and tapered to 0.2 mg/kg/day by 6 weeks. If the infant had a benign rejection history after 6 months, alternate-day steroid administration was begun in an attempt to wean the child off steroids by 9 to 12 months.

Table 1. Stanford Cardiac Transplantation Immunosuppression Regimen[a]

Drug	<1 Year	>1 Year, <14 Years
Cyclosporine		
1 Month	12 ± 8.2	10 ± 5.5
1 Year	16 ± 8.4	12 ± 6.7
3 Years	. . .	10 ± 5.6
Prednisone		
1 Month	0.6 ± 0.2	0.5 ± 0.2
1 Year	0.2 ± 0.1	0.2 ± 0.1
3 Years	. . .	0.1 ± 0.09
Azathioprine		
1 Month	1.6 ± 0.4	2.0 ± 0.6
1 Year	1.6 ± 0.4	2.2 ± 0.9
3 Years	. . .	1.8 ± 1.3

[a] Values are given in milligrams per kilogram.

The murine monoclonal antibody OKT3 was used during the first 2 weeks after transplantation. The appropriate dose was a subjective determination at first; however, with use, we have found that 0.1 to 0.2 mg/kg/day of OKT3 is adequate to diminish the T cells to less than 5%. We also believe that further depletion is not necessary and may be harmful in light of recent reports of increased malignancies [7]. Currently, we are not using any antilymphocyte preparation in infants less than 3 months of age at transplantation.

Diagnosis and Treatment of Rejection

The detection of cardiac rejection in infants relies predominantly on noninvasive means rather than the traditional cardiac biopsy technique. Due to the small size of these infants, frequent biopsies are limited due to venous access. Therefore, we rely primarily on echocardiography as a method to detect rejection. Beginning within the first week after transplantation, echocardiography is performed twice weekly. A major drop in the systolic shortening fraction as compared with a previous echocardiogram is suggestive of cardiac rejection. The diastolic parameters of increased posterior wall thickness and impaired diastolic relaxation are suggestive of cardiac rejection. These echocardiographic findings with evidence of clinical deterioration lead to the diagnosis of cardiac rejection. Before treatment, infection is excluded. Treatment consists of bolus methylprednisolone at 15 mg/kg for 3 consecutive days. Repeat evaluation occurs in 3 to 4 days. If resolution of presumed rejection does not occur, cardiac biopsy is performed before a second course of therapy is given.

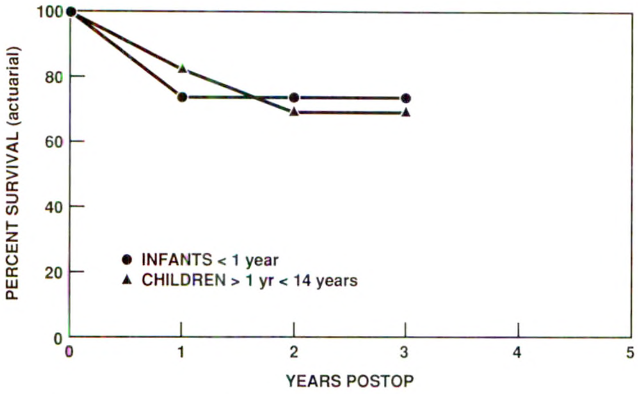

Fig 1. Actuarial survival of infants (<1 year, n = 12) as compared with children (>1 year and <14 years, n = 34).

Pulmonary rejection in this age group is based on clinical criteria. A perihilar infiltrate on chest roentgenogram, pleural effusions, dropping oxygen tension, and absence of infection on bronchopulmonary lavage are diagnostic of rejection, and therapy is instituted. Pulmonary biopsies have been attemped in this age group without success.

Statistical Analysis

Actuarial curves were computed by the method of Kaplan-Meier [8] and compared by the method of Gehan [9]. Linearized rates were compared with the maximum likelihood ratio [10]. Actuarial curves and linearized rates were expressed as the mean ± one standard deviation.

Results

Seventeen infants less than 1 year of age have undergone thoracic transplantation. Twelve infants have undergone heart transplantation and 5 infants have undergone either heart-lung or lung transplantation.

Actuarial survival at 1 and 2 years is 74.1% ± 12.9% (n = 12), with all of the deaths occurring within the first year after transplantation (Fig 1). Survival of the infants compared favorably with that of the older children, who had 1- and 2-year actuarial survivals of 82.1% ± 8.1% and 69.5% ± 10.7%, respectively (n = 32) (see Fig 1). The three deaths that occurred in the infant group were due to pulmonary hypertension, severe acute rejection, and pulmonary sepsis. The death that resulted from pulmonary hypertension occurred in an infant with HLHS. On further review of the preoperative echocardiogram, the infant with HLHS had an intact atrial septum with mitral atresia, which could possibly explain the early changes of pulmonary hypertension found at autopsy. On autopsy, this infant had grade 3 and 4 Heath-Edwards changes reflective of severe pulmonary hypertensive changes. The death due to rejection occurred 3 weeks after transplantation in an infant who underwent transplantation at 4 weeks of age for HLHS. There was no evidence of early rejection, and the infant was discharged at 2 weeks. The infant returned 1 week later with cardiovascular collapse, and severe cardiac rejection was determined on autopsy. The third death occurred due to pulmonary sepsis. This infant's postoperative course was complicated by preoperative thrombosis of the superior vena cava. This resulted in postoperative pleural effusion requiring thoracic duct ligation and pleural sclerosis. Secondary to prolonged intubation, pneumonitis developed due to resistant *Enterobacter* species with subsequent demise.

Three infants have undergone heart-lung transplantation with one death. This death occurred secondary to severe bronchial stenosis bilaterally and pulmonary sepsis. The bronchial stenosis was thought to be due to ischemia. In the immediate postoperative period, the cardiac graft had to be supported with a left ventricular assist device. This most likely resulted in poor collateral blood flow to the airways from the coronary-bronchial collaterals. Interestingly, this has been our only airway complication in more than 90 heart-lung transplants.

Two infants have received single lung transplants with one death. The death occurred secondary to resistant *Pseudomonas* pneumonia in the infant with bronchopulmonary dysplasia.

Rejection

Infants undergoing heart transplantation had fewer rejection episodes as compared with older children (more than 1 and less than 14 years). At the end of 3 months, the linearized rejection rate for infants was 0.61 events per 100 patient days as compared with 1.48 events per 100 patient days in the older group (p = not significant) (Fig 2). The lack of statistical significance was possibly due to the small numbers present in the infant group. At the end of 6 months, 51% of the infants had never rejected as compared with 24% in the older age group (see Fig 2). Although the number of events seemed to be less, the severity of rejection in the infant group was as severe as in the older children, with 1 infant dying 3 weeks after heart transplantation secondary to severe acute rejection. Another child had very resistant rejection and eventually required total lymphoid irradiation before the rejection was brought under control. Therefore, close surveillance for heart rejection has been mandated by this experience.

Pulmonary rejection has occurred as frequently in this

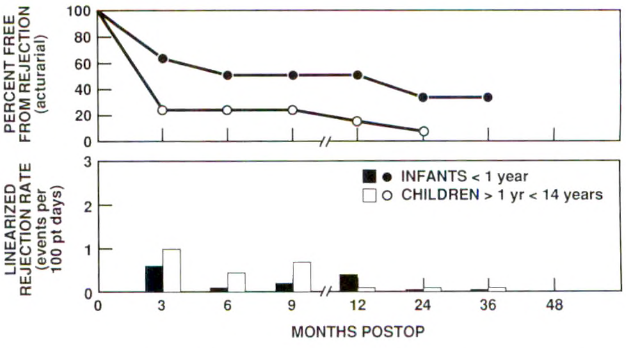

Fig 2. (Top) Percent free from rejection (actuarial) in infants versus children followed up for 3 years. (Bottom) Linearized rejection rate in infants versus children.

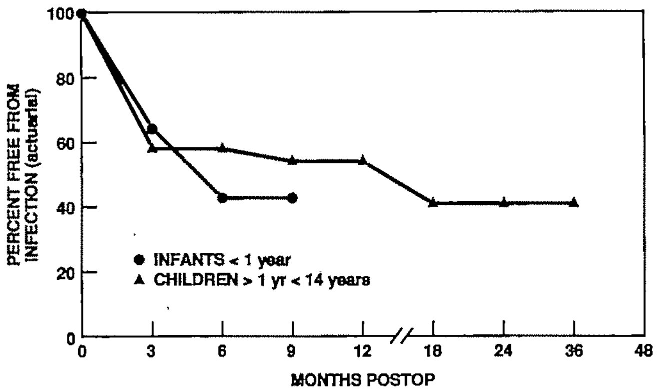

Fig 3. Percent free from infection (actuarial) in infants as compared with older children.

age group as in the older groups of patients. Of the 3 surviving infants with either heart-lung or lung transplantation, pulmonary rejection was present in all. On each occasion, the episode of rejection responded to pulse methylprednisolone therapy. In the 1-month-old infant, pulmonary rejection was noted on the tenth postoperative day, with an increasing pulmonary infiltrate, falling oxygen tension, and increasing tachypnea. Infection was excluded by bronchoaveolar lavage, making the diagnosis of rejection the most likely explanation of the infiltrate. The chest roentgenogram cleared promptly with pulse steroids.

Renal Function

Children, in general, have tolerated cyclosporine better than adults. This has also been true of the infants undergoing thoracic transplantation. Serum creatinine levels at 1, 6, and 12 months were 25.6, 28.3, and 31.8 μmol/L (0.29, 0.32, and 0.36 mg/dL). Five infants with follow-up greater than 18 months had a serum creatinine level of 31.8 ± 9.7 μmol/L (0.36 ± 0.11 mg/dL) and demonstrated no evidence of renal compromise.

Allograft Function and Coronary Anatomy

At subsequent evaluation either by echocardiogram or by catheterization at annual follow-up, there was no evidence of suture line stenosis, cardiac indices were normal, and the left ventricular end-diastolic pressure was 7.1 ± 1.2 mm Hg. There was no evidence of coronary disease in the infants in either the heart or heart-lung transplant group. The absence of coronary disease to date in this group compares favorably with the 20% incidence in the older age group.

Complications

The complication of infection in this age group has been no more frequent than in the older children (Fig 3). As noted in Figure 3, only 40% of infants remained free of infection at the end of 1 year. The distribution of infection between bacterial, viral, and fungal was no different than noted in the older children.

The lymphoproliferative syndrome was noted in 2 infants. On each occasion, the tumor was associated with the Epstein-Barr virus. In both children, the tumor occurred within the first year after transplantation. Treatment in each child included a substantial reduction in immunosuppression and intravenous acyclovir administration with resolution of the tumors. One child has been without tumor for 3 years and the other child for 2 years. Follow-up has included magnetic resonance imaging every 6 months to exclude recurrence of the tumor. Obliterative bronchiolitis has not been detected in the 2 infants with heart-lung allografts who are now greater than 2 years after transplantation. Both children are without any physical restrictions.

Comment

Heart transplantation and, more recently, heart-lung and lung transplantation have been performed in infants with severe forms of congenital heart disease and cardiomyopathies with increasing frequency and success [11, 12]. The actuarial survival of 74% at 1 year was equal to our survival in older children. As noted previously, the deaths occurred in the first year after transplantation due to rejection, pulmonary hypertension, and pulmonary infection. The deaths due to pulmonary hypertension and rejection were unexpected. Severe pulmonary hypertension in the newborn period must be relatively uncommon; yet, this infant, after transplantation for HLHS, had advanced changes of pulmonary hypertension on autopsy. Retrospectively, this infant had an intact atrial septum with mitral atresia, which has an association with pulmonary hypertension, and may represent a high-risk group [13]. Rejection in the newborn has been reported to be less common. Further, some groups believe the newborn to be somewhat immunologically privileged as an allograft recipient [14]. In our current group of infants, the linearized rate of rejection was indeed less than in the older children (0.61 versus 1.48 episodes per 100 patient days). We noted, however, 2 infants with particularly resistant rejection and 1 infant who succumbed to acute severe rejection. Therefore, postoperative surveillance for rejection has to be performed with equal diligence as in the older groups.

Donor availability continues to be one of the major limitations to performing more thoracic transplantations. This limitation certainly has to be considered when one evaluates infants with severe congenital malformations, such as HLHS, where palliation may be an alternative. Over the past 3 years, 30 infants with HLHS have been seen for surgical management. Ten families selected transplantation as their first option. Of the 10, only 4 infants underwent transplantation owing to the shortage of suitable donors. The remaining 6 underwent successful palliation with the first-stage Norwood procedure. We have developed a flexible program where both options are offered in an attempt to not bias the parents. In fact, due to the frequency of HLHS, it is not possible to perform transplantation in all of these infants.

Our experience with heart-lung and lung transplantation in infants has been limited. Three infants have undergone heart-lung transplantation and 2 infants have undergone single lung transplantation. This initial experience has been encouraging. Three of 5 infants have survived and are free of complications. The airways have grown, there has been no evidence of obliterative bronchiolitis, and pulmonary rejection and infection have been relatively easy to control. The concept of lobar transplantation from older donors into small children has been applied in this initial experience with encouraging results. We believe that this will increase the potential donor pool for children needing lung transplants. Our current application involves transplanting the left upper lobe from a 2-year-old donor weighing 15 kg into the left chest of a 4-week-old recipient weighing 3 kg. This infant would have died on ECMO had the lobar transplant not been considered.

Optimal immunosuppression remains controversial. The concern over poor growth of infants on corticosteroids has influenced most centers to try protocols void of steroids. This has produced the desired result of better growth, but at what cost? Are we actually placing these infants at increased risk for other complications not so readily detectable, for example, coronary artery disease? The answers to these questions are still debated. Each center has reported its experience with various protocols as we have, but the optimal immunosuppressive protocol remains to be defined [5, 11]. Unique to the newborn may be a somewhat immature immune system or, more appropriately, a circulating suppressor cell population that may be beneficial [15, 16]. Therefore, profound T cell depletion in the newborn period may be deleterious. Based on these theoretical arguments, we have deleted antilymphocyte preparations in infants less than 3 months of age. The noted lymphoproliferative syndrome that occurred in 2 infants who had received rabbit antithymocyte globulin and OKT3 as induction therapy may represent too much immunosuppression. In fact, 1 child remains only on a small dose of cyclosporine, with serum levels of 25 to 30 ng/mL.

We believe these data support continued thoracic transplantation in infants with end-stage cardiopulmonary disease. Optimal management will involve the options of heart, heart-lung, and lung transplantation. Palliative procedures will continue to have a role in the management of some of these infants with congenital heart disease owing to a shortage of suitable donors.

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Coronary Artery Endothelial Cell and Smooth Muscle Dysfunction After Global Myocardial Ischemia

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We hypothesized that coronary artery endothelial cell function and smooth muscle function are modified by global myocardial ischemia and used bradykinin-induced secretion of endothelium-derived relaxing factor as a marker of endothelial cell function. Bradykinin and sodium nitroprusside together determined maximum smooth muscle relaxation. Potassium chloride–induced contraction determined smooth muscle contractility. Endothelium-mediated smooth muscle relaxation expressed as a ratio of total coronary smooth muscle relaxation before and after ischemia quantified endothelial cell function. The effect of global normothermic ischemia on in situ coronary arteries from 7 swine hearts was studied. Coronary arterial rings taken from 0 to 220 minutes of ischemia at 20-minute intervals were studied in vitro. The data revealed unexpected tolerance of endothelium-mediated relaxation to ischemia. Endothelium-derived relaxing factor function was maintained to 160 minutes and smooth muscle function, to 120 minutes of ischemia. Coronary artery dysfunction seen in other studies after less ischemia may be the result of injury introduced during reperfusion, may be the consequence of myocardial injury, or may be due to events operative at the level of small arterioles.

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There is increasing interest in studying the effects of cardiac ischemic and reperfusion injury at the cellular level (ie, on cardiomyocytes and vascular endothelial and smooth muscle cells) to intervene at that level. Injury to the myocyte by ischemia and reperfusion is well described. Less is known about the effects of ischemia and reperfusion on coronary artery endothelial cell function and smooth muscle function.

Endothelial cell injury during ischemia and reperfusion has been implicated in the generation of oxygen free radicals, platelet aggregation, and thrombosis and may be a mediator of myocardial reperfusion injury. Endothelial cells also produce neutrophil chemoattractants when subjected to hypoxia [1] and may be the target of leukocytes activated during ischemia with subsequent adhesion initiating reperfusion injury [2].

Ischemic and reperfusion injury is frequently described as the cumulative effects of both insults. Histological and functional data [3–5] have been interpreted to indicate that ischemia causes less injury to coronary endothelium than ischemia and reperfusion combined. Although there is species variation in endothelial cell susceptibility to ischemia [6], endothelial cells remain histologically intact for long periods of ischemia and are more tolerant of ischemia than are myocytes [7].

This study was designed to test the hypothesis that coronary artery endothelial cell function and smooth muscle function are resistant to prolonged ischemia when not subjected to physiological reperfusion. To study endothelial cell ischemic injury, vasorelaxation mediated by pharmacologically stimulated release of endothelium-derived relaxing factor (EDRF) was used as a biological assay of endothelial cell function after global myocardial ischemic injury. Release of EDRF may be a means by which myocardial blood flow is regulated, especially during low flow or hypoxic episodes. A defect in this autoregulation mechanism during ischemia and reperfusion could contribute to the "no-reflow" phenomenon. Smooth muscle contractile and relaxant function was also tested.

Material and Methods

Seven swine weighing 25 to 35 kg were sedated with intramuscular acepromazine (1.1 mg/kg) and ketamine hydrochloride (22 mg/kg) and anesthetized with sodium pentobarbital (30 mg/kg). After intubation and heparinization (30 U/kg), rapid cardiectomy was performed. A segment from the proximal left anterior descending coronary artery was harvested in approximately 30 seconds to serve as the preischemic control. The vessel was dissected free from surrounding tissue while in 12°C phosphate-buffered saline solution and gassed with 95% oxygen and 5% carbon dioxide. The solution had the following composition (millimoles per liter): NaCl, 119; KCl, 4.6; $CaCl_2$,

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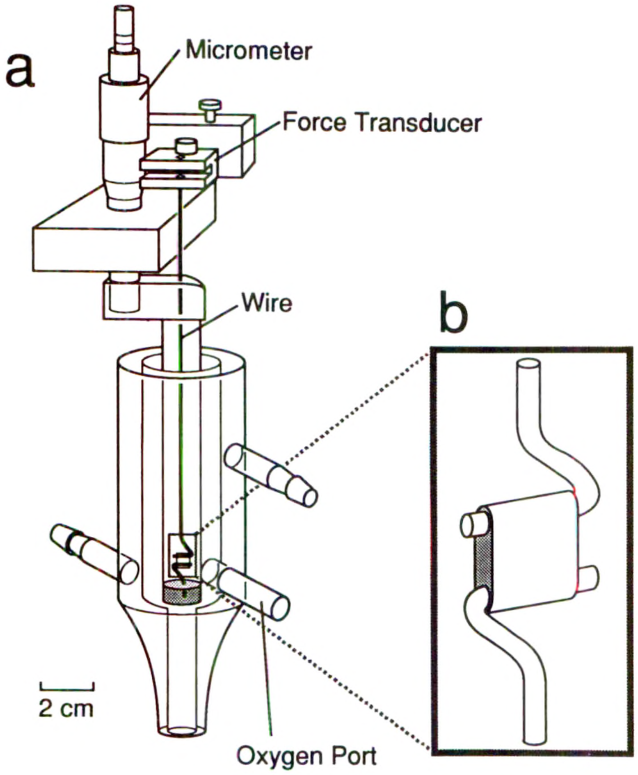


Fig 1. (a) Organ bath with strain gauge transducer. (b) Arterial ring segment mounted on wire hooks.

2.5; $MgSO_4$, 1.17; $NaHCO_3$, 25; KH_2PO_4, 1.17; EDTA (ethylenediaminetetraacetic acid), 0.027; and glucose, 11. A 3-mm length of vessel was harvested and prepared by a transverse cut using a fixed, double-bladed scalpel. The heart was sealed in a small amount of phosphate-buffered saline solution to prevent desiccation and maintained at 37°C to simulate global normothermic ischemia. Starting proximally and progressing distally, 3-mm segments of the left anterior descending coronary artery were harvested from the ischemic heart every 20 minutes for 220 minutes and prepared. All vessel segments were free from clotted blood.

A variation of this protocol was followed for 2 of the 7 hearts. Two ring segments were taken from 1 heart at times 0, 20, 40, 60, 80, 100, and 120 minutes. One of the two segments obtained at each of these times was denuded of endothelium by gentle rubbing of the tips of jeweler's forceps on the endothelial surface with care taken not to damage the smooth muscle. From the other heart, two ring segments were taken at times 0, 40, 80, 120, and 140 minutes. One of the segments was taken proximally, and one was taken from the midportion of the left anterior descending coronary artery, progressing distally on either the proximal or distal half of that artery.

All ring segments were mounted on two stainless steel wires in a 6-mL water-jacketed glass organ bath (Fig 1). The upper wire was attached to a Grass FT03D force transducer (Grass Instrument Co, Quincy, MA). The lower wire was fixed to a plastic leg attached to a micrometer (Mitutyo, Tokyo, Japan). Vessel segments that were not mounted immediately were stored on ice in phosphate-buffered saline solution and gassed with 95% oxygen and 5% carbon dioxide. Vessels were allowed to relax in the organ bath in oxygenated (95% oxygen, 5% carbon dioxide), normothermic, buffered saline solution for 60 minutes. They were incubated with 10 μmol/L indomethacin to prevent prostacyclin-mediated relaxation. (All chemicals were obtained from Sigma Chemical Co, St. Louis, MO.)

To standardize baseline resting tension at which subsequent tension measurements were to be obtained in vessels of varying size, a normalization procedure was performed. This procedure has been previously describing for small [8] and large arteries and large veins [9, 10]. The normalization procedure served to determine the circumference of each vessel at a pressure of 100 mm Hg.

Briefly, passive length–tension curves were obtained for each vessel by sequentially separating the wires using a micrometer. Force generated by the vessel was recorded on a Grass model 7 polygraph and micrometer setting noted at each step. Vessel tension (T) was calculated at each step from the equation $T = \text{Force}/2g$, where g is the length of the segment. Internal circumference (L) was determined from the equation $L = (\pi + 2)d + 2f$, where d is the wire diameter, and f is the distance between the wires. To ensure that the vessel was not overstretched, pressure was calculated from the tension and internal circumference after each step. When pressure was greater than 100 mm Hg, vessel stretch was released. A line was calculated that is the mathematical solution of the Laplace relation when pressure (P) is 100 mm Hg: $P = 100$ mm Hg $= 2\pi\ T/L$. Nonlinear regression was used to obtain the best exponential fit of the length–tension curve. A personal computer–based program [11] modified in our laboratory was used to determine the intersection of the length–tension curve and the line by an iterative fitting technique (Fig 2). The intersection of the curve and the line determined the internal circumference (L) the vessel would have at a transmural pressure of 100 mm Hg and was called L_{100}.

The internal circumference of every vessel was then set at 90% of its own $L_{100}(L_{90})$. The isometric force at this setting was termed the "passive" or "resting" force in the absence of constrictor tone. This means of determining resting force has been shown in previous experiments [12] to allow maximum tension development while standardizing resting tension independently from vessel size. Passive resting force was therefore determined for each vessel from its own length–tension curve and not by inaccurate or nonspecific methods, as is often the case in similar studies using isolated vessel rings.

Arterial segments were allowed to equilibrate for 15 to 20 minutes at L_{90} before the experiments proceeded. Smooth muscle function was tested using 25 mmol/L potassium chloride to contract the vessel. Bradykinin (1 nmol/L to 0.1 μmol/L) was administered until maximum relaxation was obtained to assess relaxation mediated by release of EDRF from endothelial cells. Maximum smooth muscle relaxation was measured using sodium nitroprus-

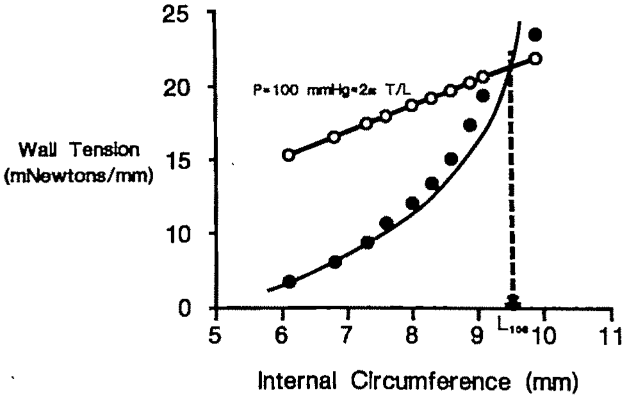


Fig 2. Normalization procedure for one arterial segment. The curved line represents the experimentally determined length–tension relationship of one vessel. It was obtained by progressively stretching the ring segment and recording tension measurements as a function of internal circumference. The best exponential fit was obtained using nonlinear regression. The straight line is the mathematical solution of the Laplace relation where pressure is equal to 100 mm Hg. The intersection of the curve and the line determined the internal circumference (L) the vessel would have at a transmural pressure of 100 mm Hg (L_{100}). (P = pressure; T = tension.)

side (1 μmol/L) in addition to 1 nmol/L to 0.01 μmol/L bradykinin (Fig 3).

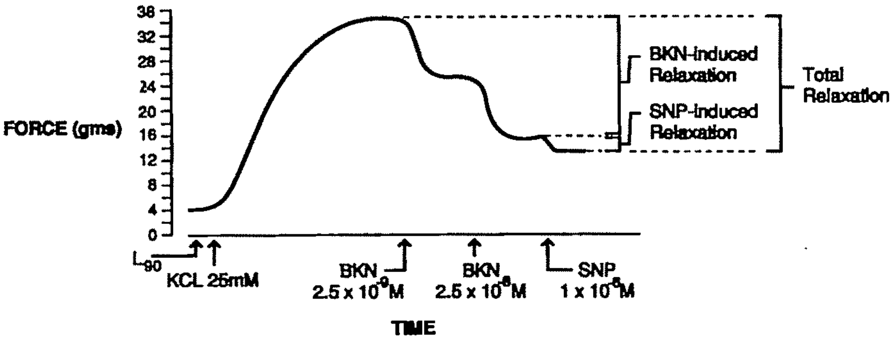
Developed pressure, calculated from the Laplace relationship ($P = 2\pi T/L_{90}$), was used to normalize tension measurements from vessels of different sizes. Mean vessel function (± standard error) for each time period was compared with preischemic control function using analysis of variance and accepting a p value of less than 0.05 as significant. The ratio of bradykinin-induced relaxation to total relaxation was calculated to separate endothelial cell dysfunction from impaired smooth muscle function. Total relaxation to sodium nitroprusside and bradykinin was calculated as a percentage of contraction to determine the effect of ischemia on smooth muscle relaxation as a function of contraction (see Fig 3). Contraction and relaxation of vessels with ($n = 6$) and without ($n = 6$) endothelium from 1 of the hearts were compared. From another heart, contraction and relaxation of five proximal epicardial ring segments were compared with contraction and relaxation of five distal epicardial ring segments. Mean functional values from the two groups with and without endothelium and from the two groups of proximal and distal vessels were comparable because each group was subject to the same ischemic injury (ie, 0, 20, 40, 60, and 80 minutes of ischemia; mean time = 40 minutes for each group).

All animals received humane care in compliance with National Institutes of Health guidelines, and the procedures and the handling of the animals were approved by the institutional animal care and use committee.

Results

Figure 3 depicts raw data plots from two representative experiments, a preischemic control vessel and a vessel after 200 minutes of ischemia. In the control vessel, potassium chloride produced a strong contraction (30 g of force). Relaxation to bradykinin was significant (18 g), and relaxation to sodium nitroprusside was relatively less (2 g) because the vessel relaxed significantly with bradykinin. In the ischemic vessel, contraction to potassium was weak (6 g). There was minimal relaxation to bradykinin (2 g) and proportionately greater direct smooth-muscle relaxation mediated by nitroprusside (2 g). A decline in the ratio of bradykinin-induced relaxation is demonstrated in

a. Control (No Ischemia)



b. 200 Minutes Ischemia

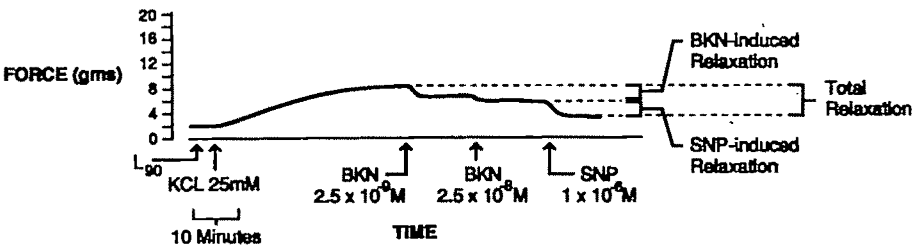


Fig 3. Raw data plots for two vessels set at L_{90}, one with and one without ischemia. (a) Nonischemic control vessel. Potassium chloride (KCL) produced a strong contraction. Relaxation to bradykinin (BKN) was significant. Additional relaxation to sodium nitroprusside (SNP) was minimal because of the strong BKN-induced relaxation. (b) Vessel subjected to 200 minutes of ischemia. Contraction to KCL was weak. There was minimal relaxation to BKN and proportionately greater direct smooth-muscle relaxation mediated by SNP than in the nonischemic vessel. Total relaxation is the combination of both BKN-induced and SNP-induced relaxation. The ratio of BKN-induced relaxation to total relaxation represents endothelium-mediated smooth muscle relaxation. A decline in this ratio is demonstrated in the vessel subjected to 200 minutes of ischemia. (L = internal circumference.)

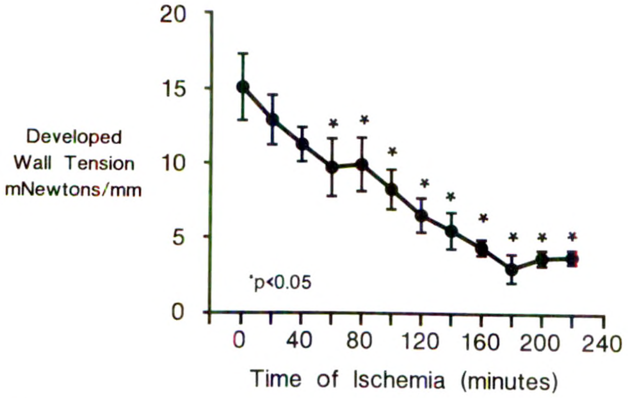


Fig 4. Coronary artery contraction induced by potassium chloride. Developed tension of potassium chloride–induced contraction was significantly decreased at 60 minutes of ischemia. This represents decrease in vessel size as well as function. Points represent mean values ± the standard error of the mean.

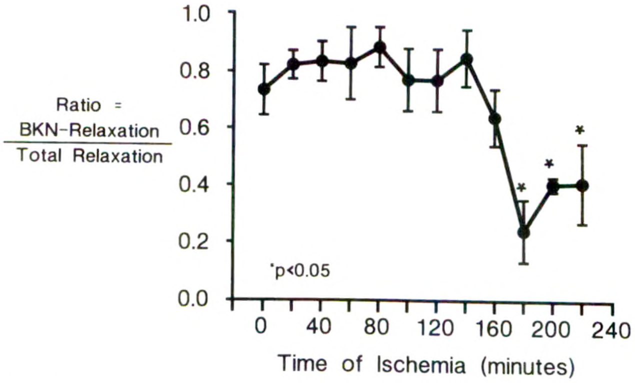


Fig 6. Coronary artery relaxation induced by bradykinin (BKN)*: endothelial cell function. Ratio of BKN-induced relaxation to total relaxation decreased significantly at 180 minutes of ischemia. This represents a decrease in endothelial cell function distinct from a decrease in smooth muscle function. Points represent mean values ± the standard error of the mean.*

the vessel subject to 200 minutes of ischemia (0.5 versus 0.9 in the control ring segment). This pattern of response is interpreted as a diminished response of the endothelium to bradykinin in a vessel with decreased contractile capacity.

Vessel Contractile Function

The graph in Figure 4 shows the decline in developed vessel-wall tension with increased ischemic time. Tension is significantly diminished from 15.1 mN/mm to 9.8 mN/mm ($p < 0.05$) after 60 minutes of ischemia. However, because of the experimental design, there was an inverse correlation of ischemic time with vessel diameter. To correct for this, developed vessel-wall pressure was calculated from wall tension to compare vessels of different size. (This is equivalent to the stress–strain analysis to assess muscle properties during diastole in intact ventricles of different sizes as compared with pressure–volume analysis.) In this analysis, Figure 5 shows that the pressure of contraction to potassium is not significantly decreased until 140 minutes compared with control vessels (from 10.8 kPa or 81 mm Hg to 7.3 kPa or 55 mm Hg; $p < 0.05$). This represents decreasing smooth muscle function. The slight increase in developed wall pressure at 200 and 220 minutes is not significantly different from 180 minutes.

Vessel Relaxant Function

The graph in Figure 6 represents bradykinin-induced coronary artery relaxation or endothelial cell function. The ratio of bradykinin-induced relaxation to total bradykinin- and sodium nitroprusside-mediated relaxation decreased significantly from 0.74 to 0.24 ($p < 0.05$) at 180 minutes of ischemia. This represents a decrease in endothelial cell function distinct from a decrease in smooth muscle function. The slight increase in function to 0.41 at 200 and 220 minutes is not significantly different from 0.24 at 180 minutes. Figure 7 illustrates that total relaxation to com-

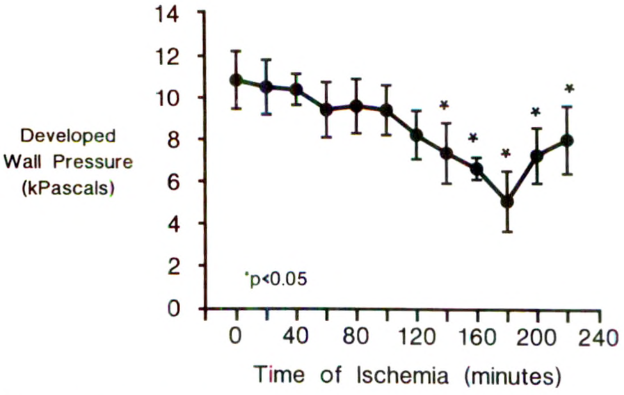


Fig 5. Coronary artery contraction induced by potassium chloride: smooth muscle function. Developed pressure of potassium chloride–induced contraction decreased with increasing ischemia. This represents decreasing smooth muscle function. Points represent mean values ± the standard error of the mean.

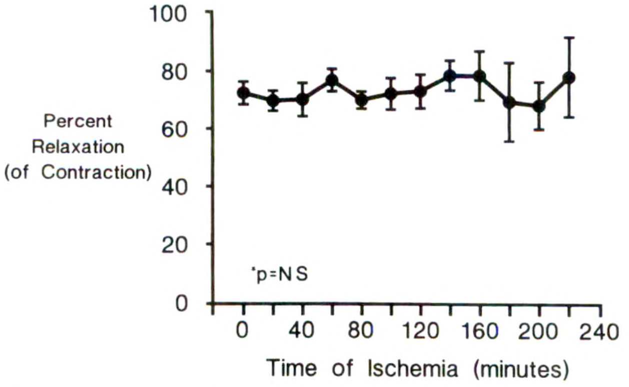


Fig 7. Coronary artery relaxation induced by bradykinin and sodium nitroprusside: smooth muscle function. Total relaxation to both bradykinin and sodium nitroprusside (percentage of contraction) was unchanged after 220 minutes of ischemia, indicating that smooth muscle relaxation may be unaffected by ischemia as a percentage of contraction. Points represent mean values ± the standard error of the mean. (NS = *not significant.)*

Table 1. Vessel Reactivity With and Without Endothelium

Variable	No. of Vessels	Pressure of Contraction (kPa)	Ratio[a]	Total Relaxation (%)
With endothelium	6	11.8 ± 1.1	0.72 ± 0.12	74 ± 4
Without endothelium	6	9.3 ± 2.8	0.23 ± 0.07[b]	93 ± 4[b]

[a] This is the ratio of bradykinin-induced relaxation to total relaxation. [b] Significance: $p < 0.05$ by analysis of variance.

bined bradykinin and sodium nitroprusside (as a percentage of contraction) was unchanged (65% to 79%) after 220 minutes of ischemia, indicating that smooth muscle relaxation as a percentage of contraction may be unaffected by ischemia. Previous studies (unpublished data) indicate sodium nitroprusside alone provides the same relaxation as nitroprusside administered after bradykinin. The relative rather than the absolute response of bradykinin-induced relaxation theoretically eliminates the influence of ischemia on smooth muscle contraction.

In vessels in which endothelium was mechanically removed (Table 1), contraction to potassium was no different from that in vessels with endothelium. Relaxation to bradykinin was significantly decreased, but total relaxation was significantly increased from 74% to 93%. There was no significant difference in distal vessel contraction, ratio of bradykinin-induced relaxation, or total relaxation compared with proximal vessels (Table 2), although there was a significant difference in size.

Comment

In this study, vasoconstriction and vasodilatation of the coronary artery were preserved after a period of ischemia during which time the myocardium is known to undergo ischemic contracture. Both arterial endothelium–mediated smooth muscle vasodilatation and direct smooth-muscle vasodilatation were preserved until 160 minutes of ischemia. After 160 minutes of ischemia, endothelial cell–mediated relaxation was lost, and only direct smooth-muscle vasodilatation was preserved. In contrast to vasodilatation, vasoconstriction was significantly reduced after 120 minutes of ischemia.

The Model

The excised heart provides a good model of global ischemia. The environment of the excised heart is similar to that during bypass grafting and transport of donor hearts in several ways. There is reduction in mechanical and metabolic activity of the myocardium when the heart is arrested. Anticoagulation with heparin sodium prohibits the effect of thrombosis on endothelial cell function [13]. The effect of myocardium-generated oxygen free radicals and neutrophil migration during ischemia was preserved because the vessels were left in situ during the ischemic period. This model, however, does not use potassium or cold cardioplegia. The injury of ischemia may be magnified, therefore, but observations remain relevant. Moreover, potassium and cold may have independent effects unrelated to ischemia that will require future study.

Smooth Muscle Dysfunction

The loss of smooth muscle contractility after ischemic injury observed in this study is consistent with the finding of decreased vascular contractility after ischemia alone in the study of VanBenthuysen and associates [3]. Both that group [3] and Ku [14] also showed increased vascular reactivity to potassium chloride (shift of dose–responsive curve to the left with decrease in EC_{50} or effective concentration causing half maximum relaxation), which was not tested in this study. Decrease in contractility with ischemia alone may be related to loss of high-energy phosphates in the smooth muscle, whereas ischemia and reperfusion combined may cause injury to endothelium and loss of its modulating influence on reactivity of smooth muscle.

Total smooth-muscle relaxation as a percentage of contraction remained unchanged after 220 minutes of ischemia, implying that for a given contraction, ischemia does not diminish smooth-muscle relaxant properties. In contrast, in vivo studies [15] have shown that coronary artery vasodilatory reserve mediated by endothelium-dependent and direct smooth-muscle vasodilatation is inhibited by ischemia and reperfusion. Coronary vasodilator reserve, however, is mediated by myocardial microvessels, which in vivo are subject to myocardial compressive forces. During ischemia and reperfusion, myocardial edema may also limit capillary filling, impairing vasodilatory reserve. The preservation of direct smooth-muscle relaxation in this in vitro study demonstrates the value of studying arteries out of their vascular bed, free from arteriolar and myocardial influences.

The importance of using L_{90} as the resting length rather than a force arbitrarily chosen is an important adjunctive finding of this study. Larger vessels required a higher optimal resting tension for maximal contraction (Table 3).

Table 2. Summary of Size Effect on Reactivity

Variable	No. of Vessels	L_{100} (mm)	Tension/Pressure of Contraction (mN/mm)	Ratio of Relaxation[a]	Total Relaxation (%)
Proximal vessels	5	3.2	12.3 ± 1.9/8.5 ± 0.8	0.92 ± 0.05	82 ± 2.4
Distal vessels	5	2.2[b]	10.9 ± 2.1/10.6 ± 1.5	0.98 ± 0.02	82 ± 1.2

[a] This is the ratio of bradykinin-induced relaxation to total relaxation. [b] Significance: $p < 0.05$ by analysis of variance.

L_{100} = internal diameter at 100 mm Hg or 13.3 kPa.

Table 3. Resting Tension at L_{90}

Ischemia (min)	No. of Vessels (mm)	L_{100} (mm)	Tension (mN/mm)
0	5	3.08	8.45 ± 0.6
20	5	2.73	8.90 ± 1.7
40	6	2.41	6.55 ± 1.0
60	5	2.24	5.59 ± 0.6[a]
80	6	2.22	6.10 ± 0.8[a]
100	6	1.92	4.41 ± 0.3[a]
120	7	1.70	3.75 ± 0.5[a]
140	6	1.62	2.76 ± 0.3[a]
160	5	1.45	3.27 ± 0.3[a]
180	5	1.27	2.86 ± 0.5[a]
200	4	1.16	2.25 ± 0.5[a]
220	3	1.10	1.96 ± 0.2[a]

[a] Significance: $p < 0.05$ by analysis of variance.

L_{90} = internal circumference at 90% of circumference at a pressure of 100 mm Hg; L_{100} = internal diameter at 100 mm Hg or 13.3 kPa.

If ring segments had been set at similar resting tensions, because of size differences some vessels may not have been set at their optimal resting tension and would therefore have developed suboptimal contractions. The manner in which the vessels were sequentially taken resulted in the larger vessels being studied after shorter periods of ischemia and smaller vessels being studied after longer periods of ischemia. Developed tension therefore became diminished at earlier time periods as an artifact of vessel size. Using developed pressure rather than tension, however, allowed comparison between vessels of varying sizes. When vessel size was normalized by using developed pressure rather than developed tension, vessels did not have significantly diminished contractions until 140 minutes of ischemia.

Endothelial Cell Injury

Histological (electron microscopic) observations on epicardial coronary artery endothelial cell damage after ischemia and ischemia with reperfusion are conflicting [3, 5, 16]. This may in part be due to sampling of smaller, intramyocardial vessels, which seem histologically to be more susceptible to ischemia and to ischemia with reperfusion injury [6, 7, 17] than large epicardial arteries. Functional assessment by the release of EDRF may be more sensitive than histological observations alone. Ischemia may affect the position of the vessel on its potassium concentration response curve. Smooth muscle response to EDRF may vary with the position of the vessel on its potassium concentration response curve. Further optimization of the potassium concentration in this study (ie, by determining and using the 50% to 80% effective concentration of potassium at each time point of ischemia), however, would be unlikely to change the endothelium-mediated portion of total smooth-muscle relaxation, as total relaxation is unchanged at any time point.

Coronary artery endothelial cell dysfunction seen in other studies [5, 16, 18] after less ischemia may be the result of injury introduced during reperfusion or may be the consequence of myocardial injury. Investigation [19] of anoxic perfused hearts shows the endothelium to be more resistant to hypoxia-reoxygenation than cardiomyocytes. Microvascular coronary endothelium has been shown to have a lower energy demand and a greater glycolytic capacity than myocardial cells and, therefore, to have greater energetic stability than cardiomyocytes under hypoxic conditions [20].

The literature suggests that smaller coronary vessels may be more susceptible to ischemic and reperfusion injury than larger vessels [4]. In the present study, however, all coronary vessels used were epicardial and thus relatively large compared with intramyocardial resistance arterioles. When developed pressure in distal epicardial vessels was compared with that in proximal epicardial vessels (see Table 2: each group had equal mean times of ischemia but significant difference in sizes), there was no difference in contraction to potassium, relaxation to bradykinin, or total ability to relax. These data suggest the response of proximal compared with distal vessels after ischemic injury is not different. These data also suggest that smooth muscle function and endothelial cell function do not vary from proximal to distal.

Effect of Removing Endothelium

When endothelium was removed mechanically, the vessels had the same decrement in bradykinin-induced or endothelium-mediated relaxation as vessels injured by 180 minutes of ischemia. The pressure of contraction was unchanged, indicating that smooth muscle contractile properties were not damaged by removal of endothelium. Total relaxation, however, increased when the endothelium was removed. This may be the result of removal of an endothelium-derived contracting factor (ie, endothelin) or greater access of the sodium nitroprusside to the smooth muscle. These effects demonstrate the complex homeostatic role of the endothelium in vessel reactivity and the importance of preserving endothelial cell function. This balance between contracting and relaxing factors of the endothelium and interaction with smooth muscle function may be more complicated in ischemic injury than simple mechanical removal of the endothelium.

Conclusion

This study examined only one of the components of ischemic and reperfusion injury, namely, global ischemia, to myocardial vascular endothelium and smooth muscle tissue. It is important to define the effects of ischemia before studying the more complex effects of ischemia-reperfusion injury on vascular function. Other studies are required to delineate ischemic and reperfusion injury to the microcirculatory endothelium and smooth muscle. Reperfusion injury must be further investigated to understand the interaction of injury to the vascular bed with injury to the myocardium itself. The factors contributing to reperfusion injury must be understood at the cellular level to intervene clinically.

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Imaged Thoracoscopic Surgery: A New Thoracic Technique for Resection of Mediastinal Cysts

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Previously, intrathoracic organs have been approached by either thoracotomy or thoracoscopy. A technique, imaged thoracoscopic surgery, using video optics and projection of images on a screen provides another option for the thoracic surgeon. Two patients with mediastinal cysts, one bronchogenic and one esophageal, underwent surgical removal using imaged thoracoscopic surgery. Postoperative pain was markedly reduced, hospitalization shortened, and recovery accelerated. Numerous complex surgical procedures can be performed using imaged thoracoscopic surgery.

(Ann Thorac Surg 1992;53:318–20)

Currently, thoracic surgeons have two basic approaches to the intrathoracic organs, which are thoracoscopy and thoracotomy. Each has certain innate, adverse characteristics. Recently, a third option, imaged thoracoscopic surgery, has become available. Two patients with mediastinal cysts were successfully treated using imaged thoracoscopic surgery.

Technique

After intubation and administration of anesthesia with a double-lumen tube, the patient is placed in the lateral decubitus position. The right side of the chest is antiseptically prepared and draped, and the right lung is collapsed. A 2-cm incision is made in the sixth intercostal space in the midaxillary line. Digital palpation is used to enter the thoracic cavity so as to avoid tearing any adhesions that might be present. A 10-mm Storz 0-degree Panview Diagnostic Telescope (Karl Storz Endoscopy, Culver City, CA), Dyonics model 5600 camera and camera head (Dyonics, Inc, Andover, MA), Dyonics Auto-Brite Illuminator II, and a Dyonics medical grade video monitor are used for visualization.

The entire intrathoracic cavity and contents are examined, and a 1.5-cm incision is made in the anterior axillary line in the fifth intercostal space. Lung forceps are passed to grasp and retract the lung anteriorly. The forceps are fixed to the skin using a towel clip. This allows excellent exposure of the cyst in the posterior mediastinum. Two 1.5-cm incisions are then made in the posterior axillary line at the fourth and sixth intercostal spaces. A spinal needle is passed through one, and the cyst is aspirated. Once fluid contents are confirmed, the cyst wall is grasped with a tonsillar clamp, and a scissor is passed through the second port and used to incise and resect the cyst down to its base (Fig 1). A benign cyst lined with mesothelial cells is confirmed by frozen section. The contents are cultured, and the mesothelial lining of the remnant cavity is sclerosed using the Birtcher Argon Beam Coagulator (Birtcher Medical Systems, Irvine, CA) [1]. A no. 20 chest tube is inserted, and all wounds are closed (Fig 2).

Case Reports

Patient 1

A 40-year-old male respiratory therapist had an extensive evaluation, including a negative laparotomy, for idiopathic abdominal pain. A small mediastinal mass had been noted on chest roentgenogram approximately 1 year earlier. Recently, it had been noted to be increasing in size. The patient denied all pulmonary symptoms. Physical examination was unremarkable except for a healed laparotomy scar. The patient refused a formal thoracotomy but did agree to imaged thoracoscopic surgery.

A soft, pliable cyst was found in the posterior mediastinum. It was opened, drained, cultured, and excised down to its base. Frozen section revealed a benign cyst with an epithelial lining and cartilaginous components. A diagnosis of benign bronchogenic cyst was made.

No special monitoring or care was required postoperatively, and his recovery was uneventful. The patient was discharged on the fourth postoperative day and has done exceedingly well. His abdominal pain has also subsided since the removal of the cyst.

Patient 2

This 31-year-old man had been in good health except for a long history of frequent seizures. During April 1991, he began to experience bronchitis with shortness of breath. A chest roentgenogram and computed tomographic scan revealed a subcarinal mass (Fig 3). Physical examination was unremarkable.

The patient underwent imaged thoracoscopic surgery. The cyst was drained and cultured, and the wall was excised down to its base. Frozen section revealed a benign cyst, and the cyst was ablated using the Birtcher Argon Beam Coagulator [2]. The patient required no special care or monitoring postoperatively, and except for a seizure on

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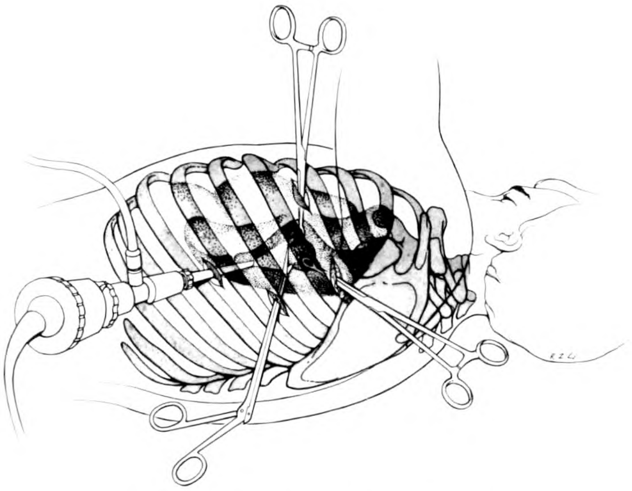

Fig 1. With a clamp holding the lung and the camera in place, the cyst is excised.

the third postoperative day, he made a very uneventful recovery (Fig 4). He was ready for discharge on his second postoperative day, but remained 3 extra days for neurological evaluation. The neurologist linked the postoperative seizure to his underlying, long history of seizure disorders.

This patient made a rapid recovery and returned to normal activity within 10 days. He continues to do well.

Comment

During the past 25 years, we have used thoracoscopy for diagnosing various malignancies within the chest, including mesothelioma [3]. Unfortunately, thoracoscopy is very restrictive, granting only limited access to the chest cavity and permitting a very confined tunnellike field of visualization for the surgeon. All other members of the operative team are excluded from participating in the procedure because they can neither see nor assist. Only the simplest diagnostic procedures can be performed [4]. Because of these limitations, thoracoscopy has been used very infrequently by thoracic surgeons. In fact, its main benefit to the patient has been the avoidance of the thoracotomy incision with its inherent pain and morbidity [5].

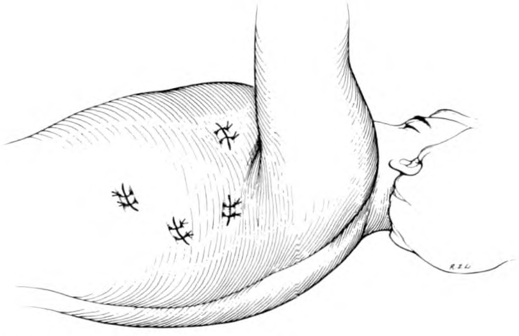

Fig 2. Postoperative incisions closed.

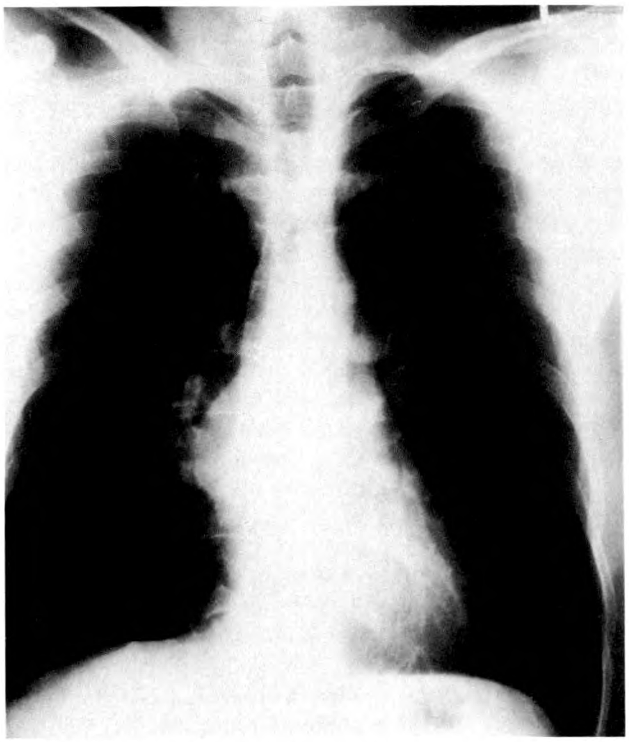

Fig 3. (Patient 2.) Preoperative chest roentgenogram shows a right mediastinal cyst.

Although the thoracotomy incision allows complete access and unlimited visualization of the chest organs,

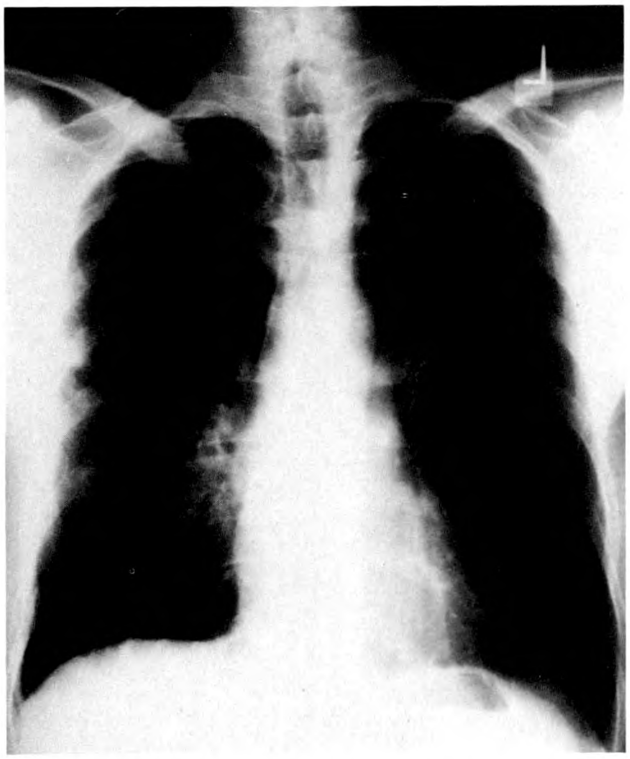

Fig 4. (Patient 2.) Postoperative chest roentgenogram.

and all members of the surgical team can readily participate, it has debilitating characteristics that can produce undesirable consequences. On occasion, because of postoperative pain, it can limit respiration and ambulation. Because many patients undergoing thoracic surgical procedures also have less than optimal pulmonary reserve, elimination of these adverse effects could be beneficial. With the advent of better optical systems that project images onto a screen, the painful thoracotomy incision, which was previously essential for exposure and access in all patients, can now be avoided in selected cases. Instead, access to the intrathoracic organs can be successfully accomplished through small ports and exposure achieved by projecting these images onto a monitoring screen. This technique, called imaged thoracoscopic surgery, enables all members of the operating team to participate in the operation. Excellent visualization of the thorax and its contents permits more advanced and complicated surgical procedures to be performed than could be accomplished with thoracoscopy.

Usually, any type of major thoracic surgical procedure is commonly followed by moderate to severe pain, prolonged recovery, lengthened hospitalization, and a probable increase in costs due to the magnitude of the intensive services required. It was our assumption that patients might derive some benefit if the traditional thoracotomy incision could be avoided in certain cases. Using the available video optics and projected images, and relying on our past experience with diagnostic thoracoscopy, it became evident that some major thoracic procedures could be safely and expeditiously performed without the added morbidity inherent to the thoracotomy incision. If the trauma to the chest wall muscles and ribs could be reduced or even eliminated, patient comfort might be improved and recovery accelerated.

In using the technique of imaged thoracoscopic surgery, it is not necessary to spread the ribs. All work is performed through the intercostal spaces, which provide adequate access to perform various surgical procedures. Usually, these same procedures would require a thoracotomy incision. Obviously, this technique is in its embryonic stages and has limited thoracic applications. Each of these patients experienced minimal pain postoperatively and seemed to make a quicker recovery. They did not require admission to the intensive care unit, and probably could have been discharged as early as their second or third postoperative day. Despite these apparent advantages, the traditional thoracic incision is still required for most surgical problems of the chest.

Because, under certain circumstances, the chest might have to be opened and the operation completed in a traditional manner, only trained thoracic surgeons should perform imaged thoracoscopic surgery. Even though this technique is more difficult and tedious to perform than operation using the traditional thoracotomy incision, its main benefit seems to result from the patients' apparent shortened recovery time. Procedures such as lung biopsy; bullous ablation; resection of benign and malignant primary tumors of the lung, recurrent pneumothorax, metastatic lung tumors, bronchial cysts, pericardial cysts, and neurogenic tumors; pericardial window; thoracic sympathectomy; truncal vagotomy; lobectomy; and pleural sclerosis for recurrent malignant effusions have already been performed using this technique. In the future, one can envision that many thoracic surgical procedures will be successfully performed by imaged thoracoscopic surgery.

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Surgical Management of Posteroseptal Accessory Atrioventricular Pathways

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From October 1988 through January 1991, 22 consecutive patients with Wolff-Parkinson-White syndrome underwent surgical ablation of symptomatic accessory posteroseptal atrioventricular pathways at our institution. As our experience with posteroseptal tracts accumulated, we found that surgical technique was logically dictated by the presence of free wall tracts and the exact location of the posteroseptal tract. Accordingly, we developed an operative approach that involves the selective use of endocardial, epicardial, and cryoablation techniques depending on the anatomic location of accessory tracts. This selective approach allows one to exploit the advantages of each technique while minimizing associated disadvantages. There were 14 men and 8 women with an average age of 25 years (range, 19 to 39 years). All patients had symptomatic tachyarrhythmias caused by accessory atrioventricular pathway(s). Most required several antiarrhythmic medications and 17 (77%) had poor arrhythmia control despite maximal medical therapy. Twelve patients had two accessory pathways and 3 also had dual atrioventricular nodal pathways. There were no early or late deaths. In 2 patients, a delta wave associated with a free wall tract reappeared 3 to 5 days after the initial operation, necessitating a second operation which successfully eliminated the accessory tract. All posteroseptal tracts were successfully eliminated during the initial operation. All patients were relieved of symptoms and are now free of medical therapy. Each patient has undergone a postoperative electrophysiologic study which confirms the absence of posteroseptal accessory conduction. The selective approach has been totally successful in our hands and should prove useful to those interested in optimizing the efficiency of surgical procedures for Wolff-Parkinson-White syndrome.

(Ann Thorac Surg 1992;53:321–5)

In the last decade, surgical techniques to ablate accessory atrioventricular (AV) conduction pathways have been refined to the point that success rates approaching 100% can be expected. It is now possible to offer patients with symptomatic Wolff-Parkinson-White syndrome a variety of safe and effective operative procedures to eliminate associated tachyarrhythmias.

Surgical ablation of accessory tracts is generally carried out by one of two basic techniques: the endocardial approach or the epicardial approach. Recently, endocardial cryoablation techniques to eliminate posteroseptal pathways [1–3] have been described.

The success rate for each of these approaches is quite high, and there appears to be no difference in the incidence of postoperative complications. Because of this, we selectively use the technique that is optimally suited for the anatomic position of the pathway. We have found that the most advantageous approach to right free wall pathways is an epicardial technique, whereas left free wall tracts appear best approached by an endocardial technique. Our specific reasons for this selective approach are described in the section entitled Recommended Approach to Posteroseptal Pathways.

Probably the most challenging tracts lie in the posterior pyramidal space [2, 4, 5]. This anatomic region of the heart has been described in detail [6] with practical emphasis being placed on the implications associated with elimination of accessory pathways in this area. Viewed from the external surface of the heart, the center of this space is marked by the middle cardiac vein, and its lateral boundaries lie approximately 2 to 3 cm to each side of the middle cardiac vein [4].

Although the division is not specifically defined in the literature, we have found it clinically useful to divide the region into three areas that are defined by the relation to the middle cardiac vein. The midseptal region is encompassed by an area approximately 1 cm on each side of the middle cardiac vein. The right paraseptal area extends roughly 1 cm to the right of the midseptal region, and the left paraseptal region lies approximately 1 cm to the left of the midseptal region. Sealy and Mikat [4] described similar regions based on the crux of the heart and found that such categorization was useful in planning the approach to posteroseptal pathways. We have preferred to use the middle cardiac (posterior interventricular) vein as the reference point because it is more precisely defined than the crux, which is an area rather than a specific point. This convention allows one to use the middle cardiac vein as a reference point to categorize posteroseptal tracts during

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intraoperative mapping. As discussed below, this type of categorization appears to have considerable clinical utility.

Posteroseptal pathways are amendable to standard endocardial or epicardial dissections, as well as the endocardial cryoablation technique. We have found that it is quite useful to have expertise in all three techniques. As our experience with the management of posteroseptal pathways has grown, we have developed a logical and successful algorithm that exploits the advantages of standard approaches while minimizing inherent disadvantages.

Material and Methods

Patient Presentation

From October 1988 through January 1991, 22 consecutive patients underwent surgical ablation of symptomatic accessory posteroseptal AV pathways at our institution. There were 14 men and 8 women. The average age was 25 years with a range from 19 to 39 years of age.

All patients had symptomatic tachyarrhythmias caused by the accessory AV pathway(s). Most required several antiarrhythmic medications for control of their tachycardia and 17 (77%) had poor arrhythmia control in spite of maximal medical therapy. Three had required previous cardioversion because of serious ventricular arrhythmias that developed from their supraventricular tachycardia.

Associated cardiac anomalies were present in 2 patients. One had Ebstein's anomaly and another had a cardiomyopathy thought to be secondary to his chronic supraventricular tachycardia. In each instance, the tachyarrhythmia associated with the accessory AV conduction tract predominated the clinical presentation.

Preoperative Evaluation

Each patient underwent a preoperative electrophysiologic study which confirmed the presence of one or more accessory pathways. Twelve patients had two accessory pathways. Three patients were also found to have dual AV nodal pathways with inducible AV nodal reentrant tachyarrhythmias.

Indications for Operation

The indications for operation included refractory cardiac symptoms or intolerance to the side effects of medication in 17 (77%). Eight patients (36%) expressed a strong preference for operation to avoid lifelong medical therapy.

The military population is unique in that regulations prohibit some individuals from remaining on active duty if a diagnosis of Wolff-Parkinson-White syndrome is made. Most of the individuals opting for surgical intervention in spite of reasonable medical control did so to remain on active duty status, and all expressed a strong preference for operation as a more acceptable option compared with long-term medical therapy.

Table 1. Operative Management of Posteroseptal Tracts

Patient No.	Location of Tracts	Operative Approach
1	Midseptal	Cryoablation
2	Midseptal	Cryoablation
3	Midseptal	Epicardial
4	Midseptal	Endocardial
5[a]	Midseptal + RFW	Epicardial
6	Midseptal + RFW	Epicardial
7[a]	Midseptal + RFW	Cryoablation (PS), epicardial (RFW)
8	Midseptal + LFW	Epicardial (PS), endocardial (LFW)
9	Midseptal + LFW	Cryoablation (PS), endocardial (LFW)
10	Left paraseptal	Endocardial (failed cryo)
11	Left paraseptal	Epicardial
12	Left paraseptal + RFW	Epicardial
13	Left paraseptal + LFW	Endocardial
14	Left paraseptal + LFW	Endocardial
15	Left paraseptal + LFW	Endocardial
16	Left paraseptal + LFW	Endocardial
17	Right paraseptal	Epicardial
18[a]	Right paraseptal	Cryoablation
19	Right paraseptal	Cryoablation
20	Right paraseptal	Cryoablation
21	Right paraseptal + RFW	Epicardial
22	Right paraseptal + LFW	Cryoablation (PS), endocardial (LFW)

[a] Dual atrioventricular node pathways also eliminated.

LFW = left free wall; PS = posteroseptal; RFW = right free wall.

General Operative Procedure

All patients underwent intraoperative mapping to identify the location of accessory tracts (Table 1). After the procedure to eliminate the pathway(s), repeated mapping along with incremental atrial and ventricular conduction studies were carried out in the operating room to confirm that the tract had been eradicated.

Table 1 reviews the operative approach used to address each of these pathways. Early in our experience we exclusively used the epicardial technique for all tracts. We found the epicardial approach to left free wall pathways somewhat cumbersome, so we then adopted the more straightforward endocardial approach to these pathways. For posteroseptal pathways, we initially used both the epicardial and the endocardial approaches, but we subsequently found that endocardial cryoablation was the easiest and most direct technique.

Epicardial Approach

Epicardial dissections were carried out using Guiraudon's technique [7–10]. An initial incision was made at the atrial reflection of the AV fat pad, and the dissection progressed along the atrial surface until the AV valve annulus was identified. A broad advance was used, encompassing the entire posteroseptal space. Sequential overlapping cryolesions (−60°C for 2 minutes) were then used to span the entire area of dissection at the level of the valve annulus. In all posteroseptal epicardial dissections the middle cardiac vein was routinely divided to enhance exposure of the posterior pyramidal space. There were no adverse sequelae associated with dividing the middle cardiac vein.

Endocardial Approach

In this well-described approach [5, 11–13], the tricuspid valve was exposed through a right atriotomy. Although some experts [11–13] use cardioplegic arrest, we have used normothermic cardiopulmonary bypass with a beating heart. A supraannular incision was made 2 mm from the valve annulus and carried from a point near the posteroseptal commissure to a point just inferior to the His bundle. This incision was carried through the right atrial wall into the AV groove fat pad, which was then dissected away from the ventricular free wall out to the epicardial reflection. The dissection was carried deep into the posterior pyramidal space and extended to the left until the annulus of the mitral valve was identified.

Endocardial Cryoablation

This technique [1–3] was reserved for posteroseptal pathways. While the patient was on normothermic cardiopulmonary bypass with a beating heart, the right atrium was opened to permit mapping around the tricuspid annulus and coronary sinus ostium. Sequential overlapping cryolesions were then placed over the area dictated by the endocardial mapping. A wide area of cryolesions was created so that 2 to 3 cm to either side of the pathway was encompassed by the cryoablation. When working near the AV node, the electrophysiologist carefully monitored for the appearance of heart block.

Results

There were no early or late deaths. Postoperative morbidity occurred in 6 patients, 4 of whom had postoperative pericarditis. In the other 2 patients, a delta wave associated with a free wall tract reappeared 3 to 5 days after the initial operation and each patient underwent a second operation, which successfully eliminated the pathway. Preoperative electrophysiologic studies indicated that each patient had both a posteroseptal tract and a free wall tract. One of these patients required an endocardial dissection of a left free wall tract that had initially been addressed by an epicardial approach, and the other required a more aggressive epicardial dissection of a right free wall tract that had initially been treated with an epicardial approach.

One other patient was found to have a right paraseptal tract during intraoperative mapping and underwent a successful endocardial cryoablation of this tract. Her postoperative electrophysiologic study confirmed the absence of the posteroseptal tract; however, a left free wall tract that had not been previously apparent was identified. Because this patient was free of symptoms and was not taking medication, she declined further therapy.

All posteroseptal tracts were successfully eliminated during the initial operation. All patients were relieved of symptoms and are now free of medical therapy. Each patient has undergone a postoperative electrophysiologic study and, except for the 1 patient mentioned previously, the electrophysiologic study has confirmed the absence of accessory AV conduction. Each of the 3 patients having an endocardial cryoablation to address dual AV nodal pathways now has no clinical or electrophysiologic evidence of dual nodal tracts.

Recommended Approach to Posteroseptal Pathways

Standard techniques used to eliminate accessory AV conduction may be selected so that the approaches complement one another. Our rationale for this algorithm is explained in this section.

Midseptal and Right Paraseptal

Midseptal and right paraseptal tracts are most amenable to endocardial cryoablation. If mapping reveals a single tract in these areas, we recommend using endocardial cryoablation as described in the previous section. This approach is the easiest and most direct way to eliminate pathways in this area [2, 3]. It avoids the often tedious dissection associated with the epicardial approach and obviates the need for making an incision into the heart, as would be necessary with the endocardial approach.

Follow-up of patients having undergone cryoablation extends from a few months to 3 years. These patients have no evidence of preexcitation, and there is no clinical or electrocardiographic evidence that cryoablation might have damaged the coronary arteries or induced automatic atrial tachycardias.

Left Paraseptal

The left paraseptal area is a transition zone between the posteroseptal region and the left free wall region [1, 4, 10, 14]. In this "gray area" between regions, we have found that an endocardial dissection is invariably effective, but endocardial cryoablation may not succeed if the pathway is at the left extreme of this region. As previously discussed, we have found an epicardial dissection to be cumbersome in this area, so we do not consider it an ideal option. For left paraseptal tracts, we place the patient on normothermic cardiopulmonary bypass and open the right atrium to carry out an endocardial cryoablation. If this is successful, then nothing more need be done. If the endocardial cryoablation fails to eliminate the tract, then we can be assured that any remaining fibers lie in the left free wall region. We then carry out a standard endocardial dissection as used for left free wall tracts.

For tracts lying in this area, it is difficult to tell whether endocardial cryoablation will be successful. Certainly the closer the tract lies to the middle cardiac vein, the greater the probability of a successful endocardial cryoablation, but the inherent margin for error in intraoperative mapping coupled with nuances in anatomy make the assessment difficult on a practical basis [4, 14]. Because the attempted cryoablation carries virtually no additional risk, we believe it is prudent to try this as a first option. If successful, it saves a patient the risks associated with hypothermia and cardioplegic arrest while allowing for a more simple operative procedure.

Multiple Pathways

When free wall and posteroseptal pathways coexist, either separately or as a broad tract that spans both regions, we address the free wall tract first. We believe that an epicardial dissection is best used for right free wall tracts, whereas endocardial dissections are optimal for left free wall tracts. Our rationale for this approach is based on our goal of using the simplest approach to accomplish the objective. This appears rational as all of the alternative approaches carry the same risk and probability of success.

For right free wall tracts, an epicardial dissection is a relatively simple operation that avoids the need for cardiopulmonary bypass and opening the heart. We have found epicardial dissections of the left free wall to be relatively cumbersome and believe that this approach creates an unnecessary risk of lacerating the coronary sinus and left atrium. In addition, coronary sinus diverticula and "atypical" posteroseptal pathways [14] can present technical problems with the epicardial approach. These concerns are obviated by using the considerably more straightforward endocardial approach for left free wall tracts. A more detailed rationale for this selective approach will be discussed in subsequent reports of our operative experience. It should be mentioned that others have come to similar conclusions [15, 16].

When right free wall tracts are found in combination with a posteroseptal tract, we recommend addressing both by an epicardial approach. The standard epicardial dissection for right free wall tracts should be carried to the middle cardiac vein [8, 9, 14], so it becomes a matter of simply extending the dissection into the left paraseptal region to complete the dissection for both pathways. This, of course, avoids cardiopulmonary bypass and opening the heart.

For left free wall tracts found along with left paraseptal pathways, the standard endocardial approach should eliminate both. In the unlikely event that remapping demonstrates a persistent posteroseptal tract, then one can be assured that it lies in the midseptal or right paraseptal region, which is easily addressed by endocardial cryoablation.

For all other combinations, we recommend approaching the tracts as two separate tracts and following the algorithm as if each tract existed alone.

If dual AV nodal tracts are to be eliminated, an endocardial cryoablation should be used for both. It is quite important to eliminate the accessory tract before addressing the dual nodal pathways. As emphasized by Cox and Ferguson [17], monitoring the AV node for the development of heart block is an essential part of cryoablative procedures to eliminate dual pathways. If the accessory tract is still present while cryolesions are being placed in the vicinity of the AV node, then conduction may occur across the accessory tract and mask the development of heart block. After intraoperative mapping has confirmed the elimination of the accessory tract, then the dual AV nodal pathways may be addressed by cryoablative procedures or a nodal dissection.

Comment

In the last decade, surgical treatment of Wolff-Parkinson-White syndrome has become an accepted mode of therapy. Posteroseptal pathways appear most difficult to eliminate [2, 4, 5], probably because of the relatively complex anatomy in this region where the four cardiac chambers are in close proximity. In contrast to the regular contours and direct operative exposure associated with free wall tracts, posteroseptal tracts require dissection into a relatively difficult anatomic area, particularly at the deep apex of the pyramidal space [6]. The endocardial cryoablation technique obviates technical challenges associated with dissection in this region while still offering the same excellent results.

Both of our patients requiring reoperation had failed epicardial dissections. In one instance a very difficult left free wall epicardial dissection had been attempted early in our experience. At reoperation this tract was easily eliminated with an endocardial resection. This case substantially contributed to the evolution of our recommended approach for left free wall tracts, which are now invariably addressed by the endocardial technique. The second case involved a right free wall tract that was initially treated with an incomplete epicardial dissection. At the time of the initial operation, there was no electrophysiologic evidence of accessory conduction after dissection of approximately three-fourths of the width of the right free wall. We mistakenly concluded the operation at that time only to find recurrence of the delta wave several days postoperatively. At the second operation, the entire free wall width was dissected, and there has been no subsequent accessory conduction. This reinforces the critically important requirement to fully dissect the entire anatomic space in which the pathway lies.

The advent of radiofrequency catheter ablation will almost certainly result in the referral of patients requiring especially difficult operations to eliminate accessory pathways. We have operated on 3 patients seen after several failed catheter ablations and have found that the surgical dissection, whether endocardial or epicardial, is considerably more difficult because of dense scarring. When confronted with such patients, we would not alter our operative plan from that which is presented here, but we would not hesitate to switch to another technique if our initial dissection proved to be dangerous because of anatomic distortions created by the radiofrequency lesions. There is little doubt that we will see more of these cases. Because these operations will be more difficult, it may be quite helpful to have the surgical versatility associated with knowledge of several operative approaches.

Clearly, any of the three standard approaches will yield a very high probability of success with a minimal complication rate. Our experience suggests that one may benefit from familiarity with each of the standard techniques. This expertise allows the surgeon to selectively employ the optimal technique dictated by the location of the pathway(s).

Our basic premise is that, because all techniques have virtually the same results, one should select the approach that is easiest to use. In most instances this will involve endocardial cryoablation, but the presence of multiple pathways or paraseptal tracts may make other choices more logical.

In conclusion, our operative strategy has evolved as experience with posteroseptal tracts has accumulated. This logical approach has been totally successful in our hands and should prove useful to those interested in optimizing the efficiency of surgical procedures for Wolff-Parkinson-White syndrome.

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Cyclosporine-Associated Central Neurotoxicity After Heart Transplantation

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Cyclosporine central neurotoxicity has been described after bone marrow, kidney, and liver transplantation but has not been well documented after heart transplantation. This case illustrates severe reversible neurotoxicity after heart transplantation with characteristic radiographic changes in magnetic resonance imaging.

(Ann Thorac Surg 1992;53:326–7)

Survival after heart transplantation has increased dramatically since the introduction of cyclosporine [1]. Unfortunately, cyclosporine therapy can be toxic to many organs including the central nervous system [2]. Although several reports have documented cyclosporine central neurotoxicity in transplant recipients, information regarding this syndrome in heart recipients is limited. We report a case of severe, yet completely reversible, central nervous system toxicity associated with cyclosporine therapy that was documented by serial magnetic resonance imaging (MRI) after heart transplantation.

A 57-year-old woman with a normal preoperative neurological and psychological evaluation underwent heart transplantation for end-stage dilated cardiomyopathy. The operation was uncomplicated. Immunosuppression consisted of 3 mg/kg of cyclosporine twice daily, azathioprine, and methylprednisolone or prednisone. The patient awoke normally and was extubated, awake, alert, and appropriately answering questions 12 hours postoperatively. Over the next 24 to 48 hours, the patient became progressively lethargic, somnolent, and difficult to arouse. With concentration, however, the patient was oriented to person, place, and time but complained of overwhelming fatigue. Electroencephalography showed diffuse slowing with no epileptiform activity.

The patient's mental status stabilized over the next few days but on postoperative day 12 her mental status acutely worsened and she became comatose. At this time the blood urea nitrogen level was 25 mmol/L (70 mg/dL) and the creatinine level was 239 μmol/L (2.7 mg/dL). The cyclosporine level was 325 ng/mL (target range, 100 to 300 ng/mL). Serum cholesterol level at this time was 3.44 mmol/L (133 mg/dL) with a low-density lipoprotein level of 1.58 mmol/L (61 mg/dL) and high-density lipoprotein of 0.85 mmol/L (33 mg/dL). The serum magnesium level was within normal limits. An extensive neurological work-up was performed. Lumbar puncture was unremarkable. Computed tomographic scan of the head was normal, but an MRI scan revealed multiple areas of increased water uptake in the white matter of essentially the entire brain. Cyclosporine administration was empirically stopped when no other cause could be determined. Over the next 2 weeks the patient gradually improved to the point where she was able to carry on normal conversations with only slight impairment of cognitive function and short-term memory. The improvement in mental status allowed a reinitiation of cyclosporine therapy. Within 2 days the patient again began to exhibit signs of increasing somnolence and lethargy. Another MRI scan was performed at that time. This scan, although markedly improved from the previous scan performed during her comatose state, did show substantial areas of increased water uptake in the white matter. The cyclosporine dose was again reduced, and the patient's mental status again improved.

Eight weeks after heart transplantation the patient was transferred to a rehabilitation service for intensive physical therapy. On a reduced dose of cyclosporine (2 mg/kg per day) the neurological condition completely normalized. The muscle strength lost during her prolonged neurological illness was almost completely regained. An MRI scan performed on discharge, 11 weeks after transplantation, revealed near-complete resolution of previous findings. The patient is without sequelae 6 months after transplantation.

Comment

The syndrome of cyclosporine-associated central neurotoxicity was initially reported after bone marrow [3] and kidney [4] transplantation and later described in detail in patients after liver transplantation [2]. The liver recipients demonstrated encephalopathy, seizures, and white matters changes and appeared to be at a higher risk when the total serum cholesterol level was low after transplantation. In a series of 48 patients, the 13 patients in whom central neurotoxicity developed had strikingly low levels of serum cholesterol compared with 35 patients without neurotoxicity. Although the incidence of cyclosporine neurotoxicity is not well established, the observed rate, 13 of 54 patients (approximately 25%), is consistent with a previous report by Adams and associates [5]. In patients undergoing heart transplantation, cyclosporine neurotox-

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icity has been reported but the incidence is unknown and documentation is limited to a single report [6]. This isolated report included cerebral infarctions as neurotoxic events, lacked confirmatory MRI findings, and did not report serum cholesterol levels.

The cause of the syndrome is unknown. Cyclosporine neurotoxicity has been associated with hypomagnesemia, which may lower the seizure threshold [7], but the predominant theory suggests that toxicity is related to intracellular transport of cyclosporine via the low-density lipoprotein receptor [8]. When total cholesterol or low-density lipoprotein levels are low, up-regulation of the low-density lipoprotein receptor occurs, intracellular transport of cyclosporine increases, and higher tissue levels of cyclosporine develop. Although the blood-brain barrier usually limits transport of cyclosporine, dysfunction of this membrane allows cyclosporine access to central nervous tissue with a relatively high density of low-density lipoprotein receptors, that is, the white matter. Although this complication can be devastating if unrecognized, the syndrome appears to be reversible. Furthermore, there appears to be a threshold dose in sensitive patients below which no serious central neurotoxicity occurs and cyclosporine therapy can be safely reinstituted.

In summary, this case illustrates that patients with central neurologic dysfunction after heart transplantation who have been treated with cyclosporine should be promptly evaluated with MRI, and the possibility of cyclosporine-associated central neurotoxicity should be considered. Patients with low serum cholesterol levels appear to be at increased risk for this syndrome. Withdrawal of cyclosporine and later reinitiation at a lower dose appears to be safe treatment for this disorder, and full neurologic recovery is possible.

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Cardiac Echinococcosis: Cyst Removal in a Beating Heart

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A 17-year-old asymptomatic boy from a sheep farm had a systolic murmur on routine examination. The diagnosis of *Echinococcus* cyst in the right ventricular outflow tract was made by echocardiography. The cyst was removed with success with the patient on cardiopulmonary bypass with a beating heart.

(Ann Thorac Surg 1992;53:328–9)

Primary echinococcosis of the heart is exceptionally uncommon, the incidence ranging from 0.02% to 2% of all human hydatidosis [1]. The right ventricle is only rarely involved, accounting for 8% of cases [1–3]. This article describes a case of cardiac echinococcosis involving the right ventricular outflow tract, and discusses the surgical removal of the cyst during cardiopulmonary bypass with a beating heart.

A 17-year-old asymptomatic boy was referred to Tygerberg Hospital by his general practitioner after a systolic murmur was heard over his precordium on routine examination. On examination he was a healthy 17-year-old boy from a sheep farm in Namibia. There were no signs of cyanosis. Blood pressure was 100/60 mm Hg with a pulse rate of 60 per minute and a hemoglobin level of 130 g/L (13 g/dL). Central venous pressure was normal. On auscultation he had a grade 3/6 systolic ejection murmur over his pulmonary outflow tract. His electrocardiogram showed sinus rhythm without ventricular hypertrophy or ST segment abnormality. A chest roentgenogram showed normal lung fields and cardiac silhouette. Two-dimensional echocardiogram showed normal dimensions of the atria and ventricles. A huge cystic mass measuring 3.2 × 3.7 cm was situated in the right ventricular outflow tract 1 cm upstream from the pulmonary valve (Fig 1). It caused mild right ventricular outflow obstruction with a calculated gradient of 25 mm Hg.

The patient underwent elective operation on June 28, 1990, through a median sternotomy. Cardiopulmonary bypass was initiated using a single biphasic right atrial cannula and an arterial cannula positioned in the ascending aorta. The mass could be seen clearly in the muscle of the right ventricular outflow tract (Fig 2). The area in which the cyst was situated was isolated from the rest of the heart and pericardial cavity with gauze packs, and well-functioning suction catheters were kept in the field of operation in case the cyst ruptured. Aspiration and sterilization of the cyst before its removal was not, however, performed. The heart was emptied and the right ventricular outflow tract opened on the empty beating heart at normothermia. The mass arose from the parietal band of the right ventricular outflow tract, subtotally obstructing the exit of the right ventricle. The mass was carefully dissected from the surrounding tissue and removed. The incision was closed with interrupted 4-0 Ticron (Davis + Geck, Danbury, CT) mattress sutures. The patient was easily weaned off cardiopulmonary bypass and had an uncomplicated postoperative course. He was asymptomatic when last seen 6 months later without any evidence of recurrence.

Comment

Hydatid disease of the heart is caused by the cestode tapeworm, *Echinococcus granulosus*. The life cycle of this parasite and the natural course of hydatid disease are well described [4]. Cardiac involvement is uncommon, and involvement of the right ventricle is rare. Three previous reviews contain only 14 cases (8%) of echinococcal disease of the right ventricle from a total of 171 cases [1–3]. Four of these fourteen patients died. All were operated on with cardiopulmonary bypass and cardioplegia.

We report a case in which the cyst was removed on the empty beating heart at normothermia. This technique is easy, and the myocardial contractions help to expel the cyst once the overlying myocardium has been exposed.

The diagnosis of cardiac echinococcosis can be difficult and must be suspected in any patient from sheep farming areas with a cystic tumor of the heart. The clinical picture may vary from asymptomatic to congestive heart failure [1]. Echocardiography, first shown by Farooki and associates [5] to be of value in the diagnosis of this disease, is accurate for the diagnosis, number, location, and size of cysts [6]. Pressure gradients can be calculated by the echocardiographist, and invasive studies are usually unnecessary in the asymptomatic patient; the risk of cyst rupture may be greater than the value of information provided [7]. We therefore suggest that coronary studies should be done in the symptomatic patient or when abnormalities of the electrocardiogram are present.

Operation is the treatment of choice for this condition. If the cyst is epicardial it can be removed without extracorporeal techniques [8]. However, most surgeons agree

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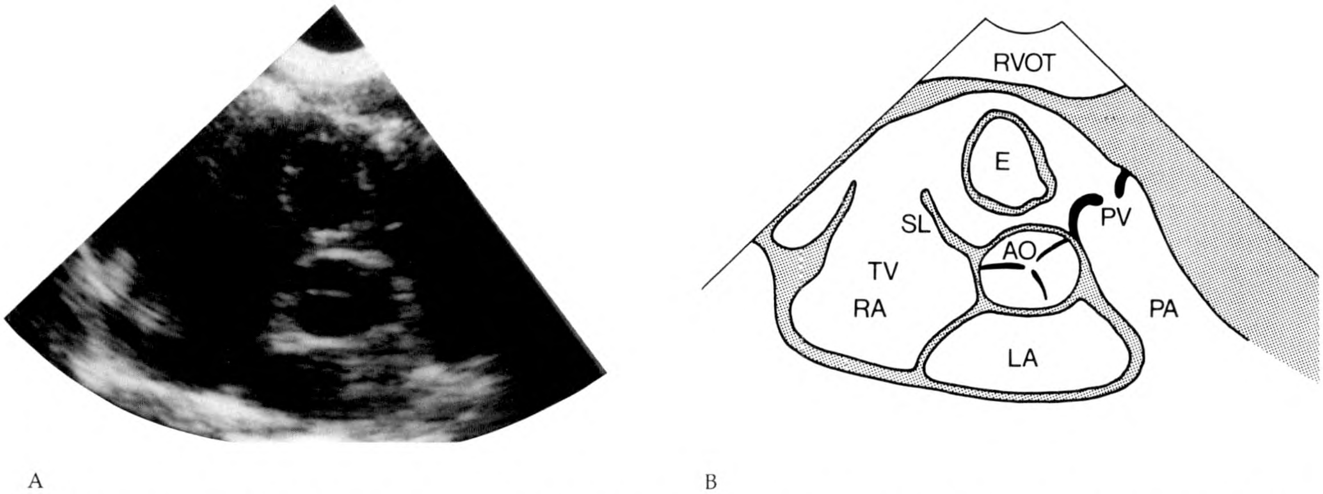

Fig 1. Echocardiogram (A) and diagram (B) of cystic mass in right ventricular outflow tract. (AO = *aortic valve;* E = Echinococcus *cyst;* LA = *left atrium;* PA = *pulmonary artery;* PV = *pulmonary valve;* RA = *right atrium;* RVOT = *right ventricular outflow tract;* SL = *septal leaflet;* TV = *tricuspid valve.)*

that this procedure should be done using cardiopulmonary bypass [3]. It is, however, possible to remove superficial cysts using cardiopulmonary bypass with an empty beating heart, as described in this report.

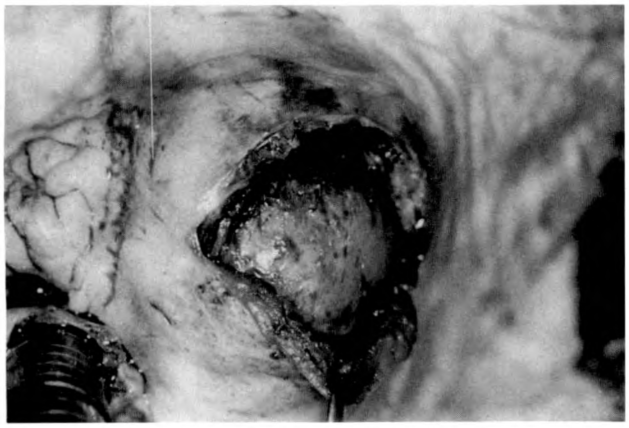

Fig 2. Mass seen in right ventricular outflow tract after exposure.

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Homograft Root Replacement for Juvenile Rheumatoid Aortic Valve Incompetence

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We report a case of severe, crippling juvenile rheumatoid arthritis and aortic insufficiency in a young woman. Homograft replacement of the aortic root offered both long-term durability and the freedom from thromboembolism that her systemic illness required.

(Ann Thorac Surg 1992;53:330–1)

Cardiac involvement in juvenile rheumatoid arthritis is a known, though uncommon, complication of the disease. Juvenile rheumatoid arthritis affects the pericardium most commonly, the myocardium rarely, and the endocardial structures so infrequently that, as of 1988, fewer than 10 surgical cases of valve involvement in juvenile rheumatoid arthritis had been reported [1]. Juvenile rheumatoid arthritis differs from the more common adult form not only in age of onset but in severity and acceleration of symptoms, seropositivity, and extraarticular manifestations [2]. The juvenile form is more malignant, but aortic valve involvement requiring replacement is still exceedingly rare. By that time, systemic manifestations may be widespread and multiple joint replacements, ankylosis, and even immobility are common. In this setting, the need for a durable prosthesis not requiring anticoagulation is obvious. We recently treated a patient with crippling juvenile rheumatoid arthritis and aortic insufficiency by replacing her left ventricular outflow tract with a fresh frozen homograft.

A 36-year-old woman was admitted with heart failure and orthopnea so severe that she slept in a chair. She was diagnosed with juvenile rheumatoid arthritis at age 6 years when her first joint became involved. Over the years, her illness progressed steadily despite a full spectrum of drug treatment including gold, penicillamine, aspirin, and steroids. She underwent bilateral hip and shoulder replacements in her 20s and 30s and had multiple contractures, ankylosis, and small joint deformities. A heart murmur was first noted at age 30 years and was monitored by serial echocardiography. Although she could not walk independently, use of a wheelchair allowed employment as a civil servant. She eventually entered the hospital because she could only sleep sitting bolt upright. An occasional ibuprofen tablet was her only medicine.

Physical examination showed a thin, almost cachectic, woman weighing 86 pounds. Her blood pressure was 110/30 mm Hg, and her pulse rate was 100 beats/min. Head-bobbing and Quincke's pulses were easily identified. She had micrognathia, keratoconjunctivitis sicca, fusion of her cervical and lumbar spine, and multiple orthopedic scars. Cardiac examination disclosed a grade 4/6 diastolic murmur, cardiomegaly, and no rales. She was rheumatoid factor– and human lymphocyte antigen B27–negative. Cineangiography showed severe aortic valve incompetence, left ventricular dilatation, and reduced contractility (Fig 1). Comparison of serial echocardiograms confirmed an accelerating degree of chamber enlargement and loss of fractional shortening. Pulmonary function tests showed a moderate restrictive defect.

An operation was undertaken in January 1991. Because of her micrognathia and dessicated mucous membranes, nasal intubation was carefully performed over a pediatric flexible bronchoscope. The ascending aorta was normal morphologically. The pericardium was thickened but free of adhesions. The trileaflet aortic valve was inflamed and contracted, and it lacked rheumatoid nodules. The valve was excised and the entire root was replaced with a 20-mm fresh frozen homograft using the Bentall technique (Fig 2). Microscopic examination of the valve showed nonspecific inflammation with lymphocyte infiltration and no granulomas. The patient recovered uneventfully and was discharged home on the sixth postoperative day.

Comment

Aortic valve replacement in the setting of juvenile rheumatoid arthritis has rarely been reported [3]. A wide range of immune-mediated arthropathies exist, and nearly all can affect the heart to varying degrees [4]. The juvenile form of rheumatoid arthritis is rheumatoid factor–negative, unlike adult diseases [2–4]. As such, the valve is usually free of rheumatoid nodules, although even in adults with seropositivity, the typical histologic pattern shows a valve destroyed by nonspecific inflammation [5]. Our case likewise showed no granulomas microscopically.

The more common clinical picture of aortic insufficiency, a dilated root, and arthritis, especially in male patients, falls under the broad category of seronegative spondyloarthritidies [6]. The pathologic dilatation of the aortic annulus results in valve incompetence, rather than a direct destruction of the valve tissue by an inflammatory process. However, rheumatoid arthritis, adult or juvenile,

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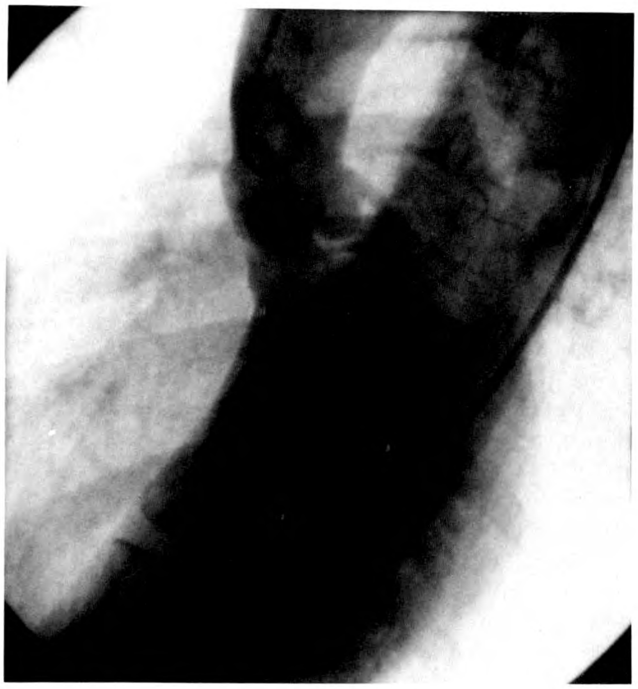

Fig 1. Aortic root injection showing a normal ascending aorta, valvular insufficiency, and chamber enlargement.

can lead to arteritis anywhere, including the aorta [1, 2]. This in part contributed to our decision to excise potentially diseased tissue and use a homograft to replace the aortic root. Consideration was given to performing a "Ross switch," or pulmonary autotransplantation, but fear of subsequent rheumatoid destruction of the transplant itself eliminated this option.

This young patient had multiple prosthetic joints and could not have taken warfarin sodium. Her life expectancy is unknown. However, a second cardiac operation to replace a degenerating porcine valve would probably not be tolerated. Excising the entire proximal aortic root along with the valve virtually eliminates any potential geometric distortion of the implanted homograft that could result in aortic insufficiency [7]. It is now our procedure of choice for homograft insertion rather than subcoronary scalloping or the "mini-root" technique.

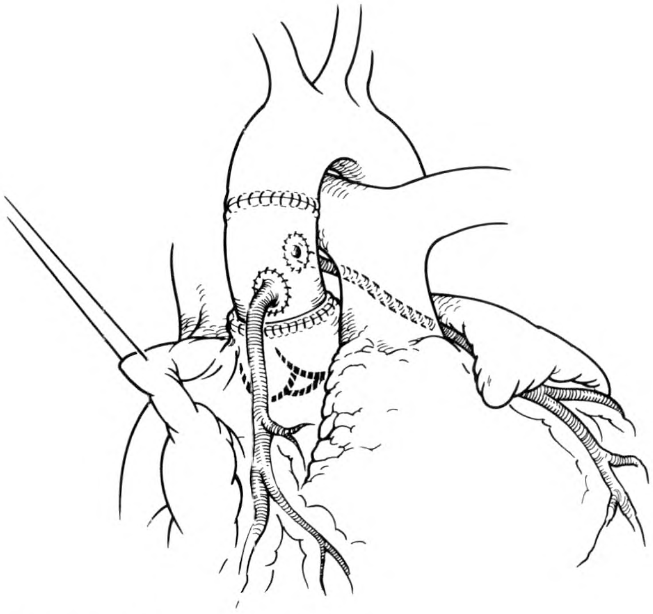

Fig 2. Completed homograft implantation.

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Long-Term Palliation of Pulmonary Artery Sarcoma by Radical Excision and Adjuvant Therapy

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The case of an extensive pulmonary artery sarcoma managed by radical excision and homograft reconstruction followed by aggressive chemotherapy and irradiation with prolonged survival is presented. Pulmonary artery sarcomas are reviewed with emphasis on the diagnosis and management of these usually fatal tumors.

(Ann Thorac Surg 1992;53:332–4)

Pulmonary artery sarcomas are infrequently encountered and usually fatal tumors. Radical excision and reconstruction using cardiopulmonary bypass followed by aggressive chemotherapy and irradiation can result in prolonged survival.

A 48-year-old woman was discovered to have a cardiac murmur on routine physical examination in January 1988, and noninvasive evaluation revealed only mitral valve prolapse. In August severe dyspnea developed along with a burning sensation in her chest while climbing stairs. Stress thallium study showed no ischemia, and a chest radiograph was normal. Physical examination revealed a single second heart sound with a harsh systolic ejection murmur at the left upper sternal border radiating to the back. Cardiac catheterization demonstrated a right ventricular outflow gradient of 45 mm Hg and a main pulmonary artery gradient of 25 mm Hg at the level of the pulmonary valve. The pulmonary valve appeared markedly thickened. No definite infundibular stenosis was identified, but the right ventricle was hypokinetic. The coronary arteries and distal pulmonary arteries appeared normal.

Operation was performed on September 30, 1988. The main pulmonary artery was noted to be enlarged with extensive neovascularity, and the arterial wall was firm to palpation from the annulus to both pulmonary arteries at the level of the first hilar branches. Palliative resection was performed with cardiopulmonary bypass. As tumor was palpable in the pulmonary annulus, a horizontal right ventriculotomy was made 1 cm proximal to the annulus and extended medially and laterally, staying just proximal to the grossly apparent tumor. The tumor was palpable posteriorly in the right ventricular outflow tract several millimeters proximal to the pulmonary annulus. The incision was completed circumferentially without injury to the interventricular septum. The right pulmonary artery was transected at the level of the truncus anterior branch, and frozen section showed no tumor at this margin. The left pulmonary artery was also transected at the level of the first branch, and frozen section showed reactive cells, possibly tumor, for which several additional millimeters of left pulmonary artery opposite this branch were resected. Reconstruction was accomplished using a 22-mm cryopreserved homograft. Her postoperative course was uncomplicated, and she was discharged on the sixth postoperative day.

Pathologic examination of the resected tumor demonstrated an exophytic sarcomatous proliferation within the pulmonary artery, arising within the intima. The media was uninvolved except for rare foci of tumor cells extending through the internal elastic lamina to involve the lamina media. The more cellular portions of the tumor, composed of cytologically malignant spindle and epithelioid cells, was located adjacent to the pulmonary lumen (Fig 1). The hypocellular, largely hyalinized portion extended distally to involve the left and right pulmonary arteries. The sarcoma had a rich network of small vessels with a concomitant lymphoplasmacytic infiltrate. Microscopic examination showed endothelial tumor involvement of the proximal right ventricular margin and both distal pulmonary artery margins. Ultrastructural and immunohistochemical study showed primitive mesenchymal tumor cells consistent with a poorly differentiated sarcoma.

Further postoperative evaluation by computed tomography of the thorax, nuclear magnetic resonance imaging of the chest, and radionuclide bone scan showed no evidence of residual or metastatic disease. The first of three courses of high-dose methotrexate with leucovorin rescue was begun 3 weeks after operation. Two weeks later she underwent concomitant doxorubicin hydrochloride (Adriamycin; Adria Laboratories, Dublin, OH) infusion chemotherapy and high-dose intraluminal radiation therapy with catheter-delivered iridium to the areas of anastomoses, and this combined therapy was repeated 4 weeks later. External irradiation of the pulmonary arteries was begun 7 weeks postoperatively using a narrow field to exclude the left ventricle and carried to a total dose of 4,500 cGy. Additional chemotherapy consisting of Adriamycin followed by dimethyltriazenoimidazole carboxamide (DTIC) was finally administered over four monthly courses completed in May 1989.

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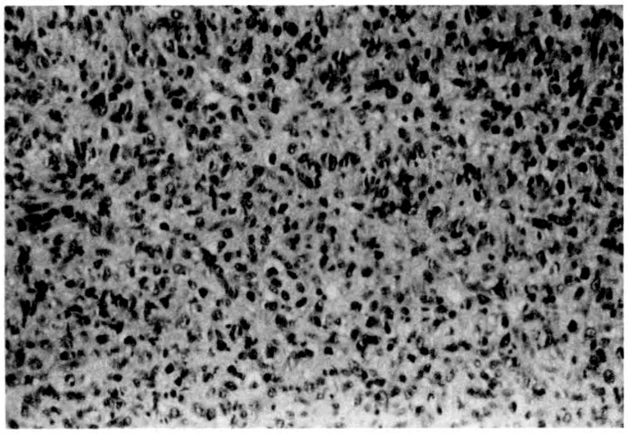

Fig 1. Photomicrograph of the more cellular portion of the tumor, showing features of undifferentiated sarcoma. (Hematoxylin and eosin; ×200 before 29% reduction.)

In October 1989 she underwent angioscopy of the right ventricular outflow tract and pulmonary arteries at the University of California, San Diego. All areas were well visualized and no tumor was seen. Computed tomography of the chest and abdomen was also performed in October 1989, and no tumor was apparent. Right heart catheterization in March 1990 showed normal right heart and pulmonary artery pressures with a 6- to 14-mm Hg gradient across the pulmonary valve and homograft. Cineangiography showed widely patent right ventricular outflow tract, homograft, and pulmonary arteries with no evidence of tumor. Echocardiogram in September 1990 showed a well-functioning homograft with a gradient of 7 to 8 mm Hg and minimal regurgitation, and a normally functioning but moderately dilated right ventricle. There was no evidence of tumor.

In October 1990, 25 months after the initial operation, she was discovered by chest radiograph to have a small solitary pulmonary nodule in the right middle lobe. Computed tomography demonstrated no other pulmonary lesions and no adenopathy, and brain scan demonstrated no systemic metastases. Right middle lobectomy was performed on November 16th. A single 1.6 × 1.3-cm nodule was found in the middle lobe, and histology confirmed it to be identical to the original sarcoma. Tumor cells were also found in the subintimal aspect of the pulmonary artery proximal to the lesion. Lymph nodes were uninvolved. Further chemotherapy consisting of three courses of VP-16 and ifosfamide followed by two courses of DTIC was administered, and she had no evidence of recurrence when last examined in November 1991, more than 3 years after initial treatment.

Comment

Since the first description of pulmonary artery sarcoma by Mandelstamm in 1923, slightly more than 100 cases have been reported in the literature. Although earlier reports were generally based on autopsy results, more recent reports have dealt with antemortem diagnosis and management of these neoplasms.

Almost all reported cases have occurred in adults with an average age of about 50 years, and there is a slight female preponderance. The diagnosis of pulmonary artery sarcomas is difficult and often delayed owing to the insidious, nonspecific nature of the symptoms. Most patients have slowly progressive exertional dyspnea, and about half complain of cough or thoracic pain. A systolic flow murmur is usually present at the left upper sternal border. Noninvasive studies are generally unrewarding. Chest radiographs are usually interpreted as normal but may show subtle abnormalities including hilar prominence, areas of pulmonary hypovascularity, or occasionally distal pulmonary metastases. Ventilation-perfusion scans may demonstrate diminished flow to one lung, and computed tomography may demonstrate a mass lesion in the pulmonary arteries. Although echocardiography has often demonstrated right ventricular dilatation, demonstration of tumor in the outflow tract or pulmonary artery has been achieved in only about 30% of reported cases. Cardiac catheterization has likewise shown right ventricular dilatation and elevated chamber pressures when there is obstruction of pulmonary arteries but has not been reliable in demonstrating the tumor.

The diagnosis of pulmonary artery sarcoma is frequently confused with pulmonary embolism. Ventilation-perfusion scans, computed tomography, and pulmonary arteriography may demonstrate an intraarterial mass but cannot distinguish between tumor and embolus. Indeed, several cases of pulmonary artery sarcoma have been encountered during operations to relieve suspected pulmonary embolus [1, 2], and the obstructive tumor and associated thrombus were usually stripped from the luminal wall through a vertical arteriotomy. Some of these cases have been complicated by serious and even fatal postreperfusion endobronchial hemorrhage [1, 2]. These resections have obviously been incomplete, and recurrence has been uniform. In a recent report magnetic resonance imaging has been shown to differentiate between pulmonary artery sarcoma and embolus using contrast enhancement of the tumor with gadolinium-diethylenetriamine pentaacetic acid [3].

Resectability for pulmonary artery sarcomas is influenced by a number of factors. Almost all of these tumors originate in the main pulmonary artery, extending intraluminally into the branch pulmonary arteries. Unfortunately almost two thirds of reported cases have had distal pulmonary tumor emboli. As symptoms are often insidious, these sarcomas are often well advanced before clinical presentation. More of these cases are also being correctly diagnosed at earlier stages of disease as the result of better methods of diagnostic imaging and heightened awareness of these tumors due to more frequent case reporting. Although many reported resections have been attempted by thoracotomy, the origin of these tumors in the main pulmonary artery suggests that a more complete resection can be obtained by a sternotomy approach using extracorporeal circulation. As the pulmonary valve and sometimes the right ventricular outflow tract may also be involved with tumor, a more radical composite resection and reconstruction may be required.

In such cases minimal manipulation of the tumor, dissection of the pulmonary arteries using extracorporeal circulation, and early transection of the distal pulmonary arteries when possible may minimize the risk of distal tumor embolization. Although combined pneumonectomy for tumor propagation beyond the first hilar branches or for the presence of recognized distal tumor emboli has been described [4–6], the higher risk of such operation for palliation should mandate very careful consideration in such cases. Even more radical resection with heart-lung transplantation has been reported [7].

Approximately one third of reported cases have had microscopic features of undifferentiated sarcomas, whereas the remainder have shown variable cellular differentiation (myogenic, chondroosseous, fibroblastic, or endothelial). Such pleomorphic diversity has suggested origin from a pleuripotential progenitor cell (myofibroblast), a concept supported by ultrastructural and immunohistochemical analyses [8]. Neither the degree of mesenchymal differentiation nor the cytologic grade of the tumor has been reported to be of prognostic value.

The results of treatment for pulmonary artery sarcomas have been discouraging as few patients survive more than a year from diagnosis. The median survival without surgical resection is 1.5 months, and this survival has been altered neither by chemotherapy nor by irradiation. Resection has lengthened median survival to 10 months, but there remain few reported cases of long-term survival. Resection and adjuvant therapy has also lengthened median survival but has not prolonged life beyond 3 or 4 years [6]. As tumor was present at the margins of resection in this case, further treatment was designed to control residual disease using a regimen of chemoenhancement (Adriamycin) and high-dose intraluminal radiation delivered to the sites of residual disease followed by external beam irradiation to the limit of surrounding heart and lung tissue tolerance. As distal microembolization of tumor was possible, adjuvant multidrug chemotherapy was also offered. Although the prognosis of these sarcomas remains poor, the palliation achieved in this case and others similarly treated in the literature [1] suggest that pulmonary artery sarcomas are best managed by multimodal treatment. Such therapy includes complete resection and reconstruction when technically feasible followed by aggressive chemotherapy and irradiation for residual disease, and adjuvant treatment for distal tumor microembolization.

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Prolonged Intraaortic Balloon Support for Septal Rupture After Myocardial Infarction

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Timing of surgical repair of ventricular septal defect developing after acute myocardial infarction remains controversial. We report the case of a 75-year-old man in whom a ventricular septal defect developed 7 days after myocardial infarction. The patient was maintained on intraaortic balloon pump support for 33 days before successful surgical closure. In the present era of aggressive preoperative hemodynamic management, the strategy of prolonged support before definitive operation on patients with myocardial infarction in whom a ventricular septal defect develops must be reconsidered.

(Ann Thorac Surg 1992;53:335–7)

Interventricular septal rupture (VSD) after myocardial infarction (MI) carries a high mortality [1–4]. Several studies advocate early (<3 days) VSD repair versus the strategy of delayed (>4 weeks) operation [1–3, 5, 6]. Early operation has been favored based on studies suggesting improved survival. It has been noted that "watchful waiting" in the 40% of patients with VSD not in shock when first seen leads in at least half of this "stable" group to cardiogenic shock [4]. The remaining patients who undergo delayed operation are thus "selected" by their less severe hemodynamic compromise. Advocates of early operation concede that the poor quality of the tissue surrounding the VSD increases operative difficulty, often requiring resection of damaged myocardium [5, 6]. An optimal solution would be to delay operation to allow healing of the compromised tissue but not at the expense of patient attrition. We report a patient with a VSD after an MI who was sustained on an intraaortic balloon pump (IABP) for 33 days before successful repair.

A 75-year-old man was seen at an outlying hospital with an inferior MI. He was ambulatory and normotensive (110/60 to 140/95 mm Hg) when at 7 days chest pain, hypotension, weakness, and a new systolic murmur developed. On transfer to Presbyterian University Hospital, he was pale, tachycardic, and tachypneic with central venous pressure of more than 20 cm H_2O and a loud systolic murmur.

A large VSD in the inferior-posterior septum by echocardiography and a 4.1:1 left to right shunt by catheterization were found (Table 1). It was elected to insert an IABP as primary therapy.

Four days later peripheral edema developed and necessitated administration of diuretics.

On day 7 after VSD, he went for routine IABP change. Within seconds of discontinuing counterpulsation, he became diaphoretic, confused, and hypotensive (systolic pressure, 50 to 60 mm Hg) (Fig 1). The IABP was reinserted. Several minutes were required before full return of systemic pressure.

On day 10 after VSD, echocardiography revealed normal left ventricular function except for akinesis of the inferior and posterior walls. On day 12 after VSD, pedal edema worsened and pulmonary congestion was seen on a roentgenogram. Dobutamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) administration was begun and maintained until operation. On day 27 after VSD, bleeding developed at the IABP insertion site requiring removal. The IABP was reinserted in the opposite femoral artery. Coronary angiography at this time showed total occlusion of the right coronary artery with minimal disease of the left anterior descending and circumflex coronary arteries.

On day 33 after VSD, the patient underwent surgical repair. The left ventricular inferior and right ventricular inferior septal walls were thin and fibrotic. A 1.5-cm-diameter hole in the inferior posterior septum with well-healed margins was oversewn with a Dacron patch. Transesophageal echocardiography showed complete VSD closure. Intraaortic balloon pump support was required for 36 hours and dobutamine for 48 hours postoperatively. Renal function was normal throughout. The patient was discharged after 45 days.

Comment

This report demonstrates the feasibility of sustained IABP support in the post-MI patient with a VSD. It must be asked whether this patient would have survived to delayed operation in the absence of IABP, ie, "self-selected." We consider this unlikely in view of the near-fatal episode during routine IABP change on day 7 post-VSD. Furthermore, dobutamine was required on day 12 and thereafter. The shunt assessed by oxygen saturation and the structural defect by echocardiography were large and unlikely to have spontaneously closed or decreased in size.

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Table 1. Hemodynamic Variables and Oxygen Saturations After Ventricular Septal Defect

Variable	Day 1 (Pre-IABP)	Day 1 (Post-IABP 1:2)	Day 7 (IABP off)	Day 7 (IABP 1:1)	Day 12 (dobutamine)	Day 18	Day 28
Hemodynamics							
RA (mm Hg)	14	13				12	8
PAP (mm Hg)	34	30				38	28
PAW (mm Hg)	19	22				21	16
SAP (mm Hg)	120/75	110/150/65[a]	90/64	55/82/40[a]		84/118/54[a]	90/115/65[a]
MAP (mm Hg)	90	88	78	60		84	80
CI (Fick) ($L \cdot min^{-1} \cdot m^{-2}$)	1.4	1.3				2.0	1.8
Systemic AVO_2 diff (vol%)	8.9	9.6				6.4	6.8
Saturations							
Mixed venous	0.54	0.49				0.46	0.59
PA	0.88	0.85				0.80	0.88
Arterial	1.00	0.99				0.95	0.99
Left-to-right shunt	4.1	3.7				3.3	3.6

[a] Systolic/diastolic augmented/lowest diastolic pressures.

AVO_2 diff = arteriovenous oxygen difference; CI = cardiac index; IABP = intraaortic balloon pump; MAP = mean arterial blood pressure; PA = pulmonary artery; PAP = mean pulmonary artery pressure; PAW = pulmonary capillary wedge pressure; RA = mean right atrial pressure; SAP = systemic arterial blood pressure.

Although it is difficult to conclude that early operation was advantageous compared with delayed operation, there is evidence that prolonged waiting was worthwhile. Despite a constant pressor dose and IABP frequency, hemodynamics improved between days 18 and 28 after VSD. This finding suggests that left ventricular function improved without a change in shunt size. Furthermore, the defect had well-healed margins allowing repair without removal of damaged tissue.

Previous studies have urged IABP support but have suggested that improvement is "short-lived" [4–8]. Most recent reports refer to the results of Gold and associates [7], in which there were 5 patients with post-MI VSD; all showed persistent dependence on IABP support [7]. This report suggested but did not present data that hemodynamic deterioration despite IABP developed in all cases. Subsequent reports have reiterated the notion of the futility of IABP for prolonged support, but the actual evidence must be considered inconclusive. This thinking has limited the use of IABP for VSD after MI, the longest period reported being 12 days [6]. It should be noted that in our case dobutamine was also necessary to optimize hemodynamics. This drug, rarely used in previous studies, may augment the ability to sustain the patient for longer periods than described previously [6].

Studies of the superiority of early as compared with delayed operation are limited by small numbers, retrospective design, nonrandomized approach, and limited patient descriptors [1–8]. Most important of the unknown aspects are the nature of preoperative hemodynamic support, hemodynamics of patients undergoing operation at various timepoints, and lack of differentiation between

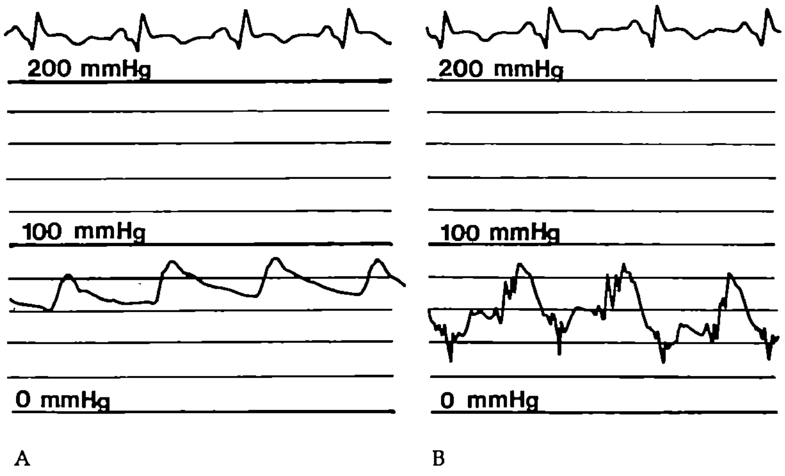

Fig 1. Rapid hemodynamic deterioration with discontinuation of the intraaortic balloon pump (IABP) on the seventh day after rupture of the interventricular septum: (A) Systemic arterial pressure immediately after the IABP was discontinued before IABP change. Note that systolic pressure is 80 to 90 mm Hg. (B) Within 60 seconds, systolic arterial pressure was less than 60 mm Hg. This figure shows the systemic pressure immediately after IABP replacement. Note that systolic pressure is now approximately 50 to 60 mm Hg. Several minutes were required until systolic arterial pressure attained the same level as before IABP change.

patients whose cardiogenic shock had been reversed by IABP versus those in whom shock was not reversible. It is clear, particularly in the era of thrombolysis, that some improvement in left ventricular function after MI often occurs. Thus, if operation could be delayed, improvement in left ventricular function in some cases might occur, which might decrease surgical risk. It should not be construed that we believe IABP support will stabilize all patients in whom cardiogenic shock develops after VSD. In those who show continued hemodynamic compromise and in whom other measures, particularly drug therapy, do not stabilize their condition, early operation may be the only option. However, it might be expected that this group will be "selected" to have a high surgical mortality [4].

Efficacy of the IABP is probably a combination of one or more of the following mechanisms: increase in coronary perfusion allowing the ischemic area around the VSD to heal more rapidly; salvage of periinfarct myocardium and improvement in left ventricular function in the infarct zone; reduction in systemic vascular resistance favoring systemic flow [5]; and improvement in right ventricular function by a decrease in right ventricular afterload if left ventricular filling pressure falls.

In the era of aggressive preoperative hemodynamic support, the possibility of prolonged IABP use in the MI patient with VSD to delayed operation must be reconsidered.

We thank Ms Sabrina Jennings for preparation of the manuscript.

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INVITED COMMENTARY

Although postinfarction ventricular septal rupture is supposed to occur in 1% to 2% of all patients who suffered a transmural myocardial infarction, fewer than 10 patients are seen each year even in large cardiac centers. Thus, it would be difficult for most of us to develop a substantial experience in the management of this complication of myocardial infarction. Nevertheless, most surgeons agree that it is not safe to operate on these patients soon after the septal rupture because of the friability of the infarcted myocardium. For this reason, these patients should initially be managed medically providing that they are well enough to be ambulatory. Unfortunately, only a few patients fall into this category. In most of them congestive heart failure or shock develops and necessitates a more aggressive treatment including intraaortic balloon pump, intravenous vasodilators, inotropes, and sometimes assisted ventilation. These patients usually improve and offer us an opportunity to perform coronary angiography and operation to correct the mechanical defect that may have caused the shock.

My colleagues and I have done so on more than 40 patients during the past decade and have learned that exclusion rather than resection of the infarcted septum with a single patch secured to viable myocardium eliminates the need to wait for fibrosis to occur to obtain a satisfactory surgical result. The septum is exposed by a left ventriculotomy through the infarcted wall; a single patch of bovine pericardium is sutured to the healthy endocardium all around the infarct with a continuous 4-0 polypropylene suture, excluding the infarcted septum and infarcted free ventricular wall from the left ventricular cavity. This patch is tailored in the same shape as the left ventricular infarct, but it is slightly larger. Minimal or no infarctectomy is performed, and the septal perforation is left alone. After the left ventriculotomy is closed, only blood from the right ventricle will contact the infarcted septum. We have used this technique in our 19 most recent patients with only one operative death. Thirteen patients were in cardiogenic shock and 11 patients had had inferior myocardial infarction.

Because of this new operative technique, we believe that the patient reported by Estrada-Quintero and associates should have been operated on the same day or on the day after the intraaortic balloon pump was inserted. To keep an elderly patient in bed with an intraaortic balloon pump, a Swan-Ganz catheter, and a regimen of inotropic agents for more than 1 month is a formidable task, not to mention the cost.

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Systemic Recombinant Tissue Plasminogen Activator Lysis for Left Atrial Thrombus Formation After Single-Lung Retransplantation

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This report describes a recipient of single-lung transplantation surviving extraordinary complications: (1) early graft failure mandating retransplantation; (2) left atrial thrombus formation, which resolved by recombinant tissue plasminogen activator lysis; (3) and development of a "locked-in-syndrome." Possible underlying mechanisms are discussed.

(Ann Thorac Surg 1992;53:338–40)

Lung transplantation has become a new challenging field in cardiothoracic surgery for patients with end-stage pulmonary disease. Since the first clinical lung transplantation performed in 1963 [1], the surgical technique has not changed substantially to this day. The postoperative management, however, is still delicate owing to a variety of difficulties predominantly related to the healing of the bronchial anastomosis, rejection, and infection [2–4].

We report on a case of right-sided single-lung transplantation with extraordinary complications including left atrial thrombus formation compromising the pulmonary venous return with resultant respiratory failure.

A 46-year-old woman suffered from progressive dyspnea, dry cough, and recurrent respiratory infections for 10 years due to idiopathic pulmonary fibrosis. In 1981 and 1985, spontaneous right-sided pneumothoraces were drained by chest tubes. In 1988, the patient required continuous oxygen supply (oxygen tension, 57 mm Hg; carbon dioxide tension, 37 mm Hg; arterial oxygen saturation, 0.91). Lung function tests showed a vital capacity of 1,150 mL (33%) and a forced expiratory volume in 1 second of 950 mL (83%). Cardiac catherization revealed mild pulmonary hypertension (pulmonary artery pressure, 34/14 mm Hg; pulmonary vascular resistance, 2.5 Wood units); left ventricular function and cardiac output (cardiac index, 3.5 $L \cdot min^{-1} \cdot m^{-2}$) were normal.

On November 2, 1989, the patient underwent single-lung transplantation on the right side, which was significantly more compromised than the left as assessed by preoperative ventilation/perfusion scan. The operation could be performed without cardiopulmonary bypass with the major omentum wrapped around the bronchial anastomosis [5]. Histologic examination of the patient's explanted lung showed chronic interstitial pneumonia and fibrosis with substantial inflammatory activity, obliterating vasculitis, and emphysema. Antibiotic prophylaxis was started intraoperatively with cefotaxime, azlocillin, flucloxacillin, and tobramycin; rejection prophylaxis was initiated by rabbit antithymocyte globulin (Ch. Bieber, Stanford, CA; 100 mg) and methylprednisolone (500 mg).

After an uneventful intraoperative and early postoperative course the patient's respiratory condition on mechanical ventilation deteriorated after 24 hours, some 12 hours after administration of antithymocyte globulin. The inspired oxygen fraction had to be increased from 0.3 to 0.6. From bronchoalveolar lavage fluid both *Pseudomonas* and *Candida* could be cultured, but despite maximal antibiotic (ciprofloxacin, amikacin) and antimycotic (amphotericin, flucytosine) treatment her lung function did not improve and she remained ventilation dependent. Transbronchial biopsy performed on day 7 showed consolidations probably resulting from adult respiratory distress syndrome, signs of viral pneumonitis (most likely cytomegalovirus), and signs of an early pulmonary rejection (vascular type). The patient was scheduled for retransplantation on postoperative day 11.

On the same day the inspired oxygen fraction had to be increased to 1.0 (oxygen tension, 65 mm Hg; carbon dioxide tension, 35 mm Hg). With a second donor organ being available, femorofemoral extracorporeal membrane oxygenation (ECMO) was instituted as a bridge to retransplantation. The patients was stabilized for 2 hours with an ECMO flow of 4 L/min (oxygen tension, 615 mm Hg) and transferred to the operating room under ECMO support. Retransplantation was performed on the right side using the same technique as during the first transplantation except for continuous ECMO support. Explant histology confirmed the biopsy findings, demonstrating widespread consolidations and adult respiratory distress syndrome (Fig 1). Postoperatively the ECMO cannulas were removed and rejection prophylaxis was initiated with

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monoclonal antibodies (OKT3; Cilag, Sulzback, Germany; 5 mg).

Seven days later, while the patient was getting ready to be weaned from artificial respiration, pulmonary function deteriorated again. Within hours, the patient again required 100% oxygen, and the chest roentgenogram showed complete opacification of the transplanted organ ("white lung"). Transbronchial biopsy showed consolidating pneumonia and signs of early rejection of the vascular type including thrombosis of small veins (Fig 2). Esophageal echocardiography revealed a large thrombus formation within the left atrium, originating from the upper pulmonary vein and extending into the atrial roof, thereby compromising pulmonary venous drainage. Systemic heparinization (partial thromboplastin time, 70 to 80 seconds) was augmented but did not improve pulmonary function. Considering the high risks of another surgical intervention, intravenous thrombolysis with recombinant tissue plasminogen activator (Actilyse) was initiated. A 20-mg bolus was followed by a 100-mg intravenous infusion for 2 hours and by 100 mg continuously intravenously for 48 hours thereafter. Within 3 days pulmonary function recurred to its prior status and the chest roentgenogram cleared to nearly normal findings. Hemorrhagic complications did not occur except for mild bleeding from skin incisions around arterial and venous lines. Control esophageal echocardiography 5 days later could not reveal any remaining thrombus formation. Pulmonary venous drainage and atrial influx were normal.

Along with the improvement in respiratory function, sedative drug administration was discontinued. However, when the patient woke up she was unable to move anything except her eyes. The muscle tone was diminished, tendon reflexes were absent, and Babinski's sign was not elicitable. There was no abnormal cervical rigidity. The clinically appearing tetraplegia was identified by neurophysiological tests as "locked-in-syndrome" of unknown cause [6]. The patient underwent tracheotomy and intensive physiotherapy. After 10 weeks she could finally be weaned from artificial respiration and was discharged from the hospital shortly afterwards. Now, 6 months after transplantation, the patient has excellent lung function (vital capacity, 1,750 mL; forced expiratory volume in 1 second, 80%), shows no neurological deficits, and is back to her job as a teacher.

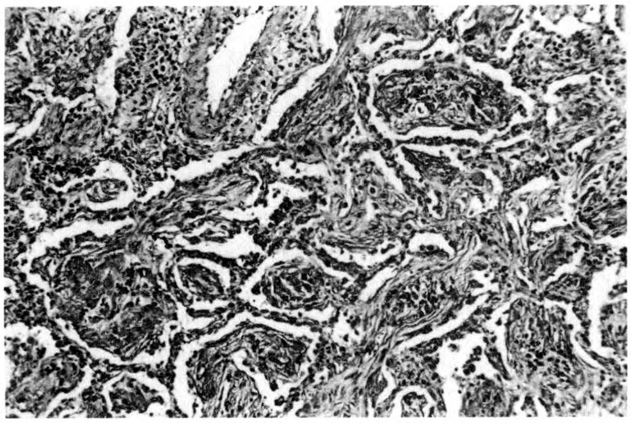

Fig 1. Explantation histology of the first transplanted lung demonstrating severe consolidating pneumonia. (Hematoxylin and eosin; ×200 before 35% reduction.)

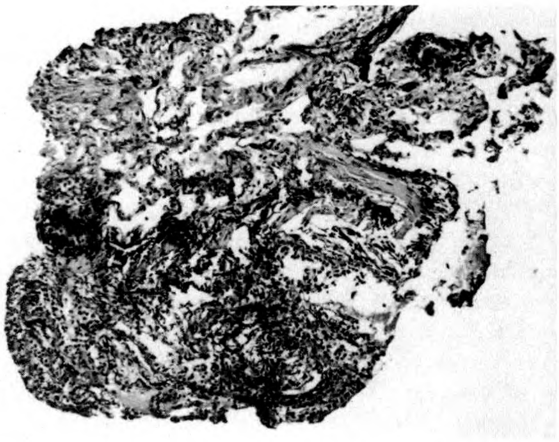

Fig 2. Transbronchial biopsy specimen of the second transplanted lung showing widespread interstitial infiltration, thrombosis of small veins, and signs of consolidating pneumonia. (Hematoxylin and eosin; ×100 before 35% reduction.)

Comment

In this case of single-lung transplantation three unusual complications deserve further discussion: early graft failure from infection, pulmonary rejection with concomitant left atrial thrombus formation, and the "locked-in-syndrome." The association of cytomegalovirus infection with an increased incidence of graft failure is known but poorly understood. It is still unclear whether infection is the primary event that precipitates rejection or whether immunosuppressive therapy used to treat rejection predisposes to an increased secondary infection. During the deterioration of the first transplanted lung we saw this coincidence in our transbronchial biopsy specimens also. However, there was no clear-cut evidence supporting either hypothesis.

After retransplantation early graft failure developed again. Now transbronchial biopsy showed signs of pulmonary rejection associated with a disseminated thrombosis of small pulmonary veins. Furthermore, esophageal echocardiography revealed a left atrial thrombus extending into the upper pulmonary vein. One may conclude that pulmonary rejection led to thrombosis of small pulmonary veins and that the left atrial thrombus formation was a result of propagated thrombus growth originating in these small pulmonary veins. Based on such an assumption, thrombolysis using recombinant tissue plasminogen activator was initiated rather than surgical removal of the thrombus. No bleeding complication occurred despite the patient's history of two previous thoracotomies and lung transplantation.

Another particular finding in this patient was the development of a "locked-in-syndrome." This severe neurological complication is mainly due to bilateral lesions of the ventral pons after ischemia or rapid alteration in serum electrolyte concentrations, which causes a pontine myelin degeneration of corticobulbar and corticospinal tracts [7]. As a result the patient is tetraplegic, unable to speak, and incapable of facial movement. The state may resemble coma, but the eyes are open and move, and the patient is fully conscious [8]. No specific therapy is possible. Fortunately, it turned out to be completely reversible in our patient. Whether there was any relationship to the atrial thrombus formation or to cerebral embolization must remain speculative as no severe postoperative serum electrolyte imbalance had occurred.

The recent success in lung transplantation is encouraging. With increasing experience and successful management of deleterious complications, the results after lung transplantation will further improve and this treatment modality may be offered to more patients with end-stage pulmonary disease.

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Mitral Valve Repair in Patients on Chronic Hemodialysis

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Two cases of successful mitral valve repair in patients on chronic hemodialysis are presented. We stress that valve repair is preferable to valve replacement whenever feasible because of improved left ventricular function, reduced complication rate, and freedom from anticoagulation. This especially applies to patients on chronic hemodialysis as they have impaired immunological function, are subjected to repeated fistula punctures with possible bacteremia, and are more susceptible to early calcification and degeneration of tissue valves.

(Ann Thorac Surg 1992;53:341–2)

Only 16 cases of mitral valve operation and 4 cases of combined aortic and mitral valve operation have been reported in patients with end-stage renal failure; the majority of the procedures (17 of 20) were mitral valve replacements [1–4]. There is little reported experience on mitral valve repair in patients with chronic renal failure. Of the 3 mitral valve repair patients described in the literature, 1 had an open mitral valvotomy for mitral stenosis, another had an insertion of a Carpentier ring for combined mitral stenosis and regurgitation, and the details of repair were not described for the third patient. We present 2 patients with mitral valve disease and chronic renal failure on hemodialysis in whom repair of the mitral valve was performed.

Case Reports

Patient 1

A 47-year-old man was admitted to our unit with a history of dyspnea on effort and in New York Heart Association functional class III. He had adult polycystic kidney disease that had progressed to end-stage renal failure 10 months before admission, and was on hemodialysis three times a week. Two-dimensional Doppler echocardiography showed mitral valve prolapse with severe mitral regurgitation. Cardiac catherization confirmed severe mitral regurgitation and normal coronary arteries. Inspection of the mitral valve at operation revealed ruptured chordae tendineae of the anterior leaflet and a dilated mitral annulus. A triangular segment of the anterior leaflet was resected and resutured, and then annuloplasty was performed with a 31-mm Duran flexible ring. Intraoperative transesophageal echocardiography performed after termination of cardiopulmonary bypass showed minimal mitral regurgitation. Dialysis was performed the day before operation and on the third postoperative day.

Patient 2

A 57-year-old woman in end-stage renal failure and on chronic hemodialysis for 4 years was seen in New York Heart Association class III clinical status. She was known to have rheumatic heart disease on follow-up for the last 8 years. Two-dimensional echocardiography showed severe mitral regurgitation, moderate tricuspid regurgitation, and mild aortic regurgitation. At operation, inspection of the mitral valve showed commissural fusion, calcification of the anterior lateral commissure, and retraction of the anterior papillary muscle. Mitral commissurotomy, anterior muscle papillotomy, commissural decalcification, and pericardial patching of an area of defect on the anterior leaflet was performed. The mitral annulus was remodeled with a 29-mm Duran flexible ring, and tricuspid annuloplasty was achieved with a 31-mm Duran flexible ring. Intraoperative transesophageal echocardiography done after termination of cardiopulmonary bypass showed the repair to be satisfactory. Dialysis was performed the day before operation and on the second postoperative day.

In both patients the postoperative course was uneventful, and they were discharged on the 13th and 12th postoperative day, respectively. Both patients were anticoagulated for 2 months with low-dose warfarin, keeping the thrombotest at approximately two times the international normalized ratio, after which anticoagulation was stopped. At 6 and 7 months after operation both patients are well and in New York Heart Association class I and II, respectively.

Comment

With the increasing population of patients on chronic hemodialysis, more patients in end-stage renal failure will require open heart operations. As open heart operations in these patients can be performed safely with satisfactory results [1], indications for operation should be similar to those in patients with normal renal function, especially before ventricular decompensation occurs. Careful and

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meticulous preoperative management of fluid replacement, electrolyte balance, and bleeding tendencies are important. We dialyze our patients on the day before operation and subsequently on the second or third postoperative day, according to serum creatinine, potassium, and pH levels. Antibiotic prophylaxis is similar to that in patients without renal disease. Strict precaution is taken in positioning the patient during operation to avoid pressure to the site of the arteriovenous fistula as thrombosis of the fistula is a reported complication in such patients [3]. At operation, every effort is made to preserve the native valve.

Patients with end-stage renal failure on chronic hemodialysis are at a higher risk for complications after open heart operations and valve replacement. These patients are known to have impaired immunological function. They are also subjected to repeated fistula punctures with possible bacteremia from the vessel access site. The presence of a prosthetic valve exposes them to an increased risk of infective endocarditis. Tissue valves implanted in patients on chronic hemodialysis have been reported to be more susceptible to early calcification and degeneration [5]. Anticoagulation mandated by the use of a mechanical valve can pose additional problems during chronic hemodialysis.

Mitral valve repair is clearly preferable to valve replacement whenever feasible in view of the well-documented advantages of improved left ventricular function, reduced complication rate, and freedom from anticoagulation. We advocate mitral valve repair when this can be safely performed, especially in patients with chronic renal failure or on hemodialysis, in view of the added advantage of retaining the native valve in such patients.

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Benign Schwannoma of the Esophagus Presenting as a Giant Fibrovascular Polyp

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The case of a 62-year-old man with benign schwannoma associated with a giant polyp of the esophagus is presented. His initial symptom was dysphagia. The polyp was removed through cervical esophagotomy. He had no recurrence of symptoms 5 years after this procedure. Pathologic examination showed a rare histology.

(Ann Thorac Surg 1992;53:343–5)

Benign schwannomas of the esophagus are rare. They usually arise close to the cricopharyngeus muscle. Symptoms include dysphagia and regurgitation of the fleshy mass in the mouth, which can cause asphyxia. Blood supply is variable; therefore, a large polyp should be removed by a surgical procedure rather than endoscopy.

A 62-year-old man with abdominal pain and dysphagia was transferred from another hospital. His medical history showed ethanol abuse, peptic ulcer disease treated with subtotal gastrectomy and Billroth II anastomosis 34 years before admission, a transthoracic vagotomy for marginal ulcers 24 years earlier, and two cervical esophagotomies for removal of polyps, the first 23 years and the second 9 years before admission. Pathology of both tumor resections showed a histologic appearance of a benign schwannoma.

A generally benign physical examination showed a cachectic, elderly man in no acute distress. He was afebrile with normal vital signs. His chest roentgenogram was normal.

An upper gastrointestinal series (Fig 1) showed a large, pedunculated, cervical esophageal mass and the previous

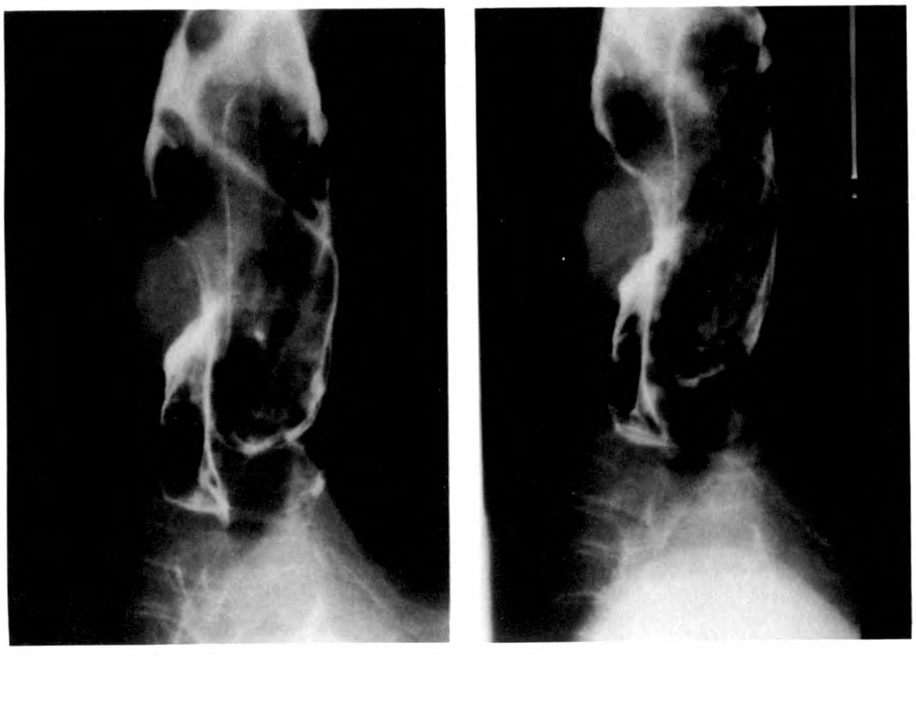

Fig 1. Upper gastrointestinal series showing a large, pedunculated cervical esophageal mass.

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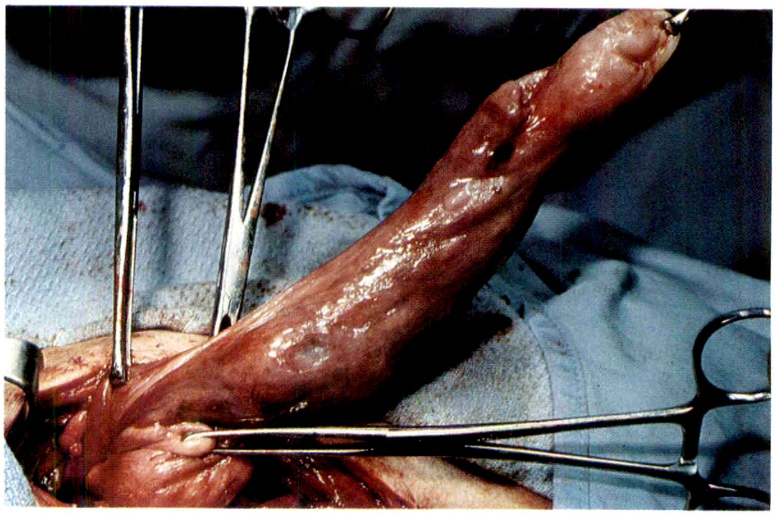

Fig 2. Intraoperative photograph of the large pedunculated mass being delivered through a left neck cervical esophagotomy.

hemigastrectomy and anastomosis. Endoscopy and biopsy showed esophageal squamous mucosa with focal basal cell hyperplasia and no evidence of malignancy.

A cervical esophagotomy was performed through a left neck incision and a large pedunculated mass measuring 14 × 4 × 2.5 cm was encountered. Its base was just below the cricopharyngeus muscle (Fig 2). The entire polyp was delivered through the incision (see Fig 2). The base and the feeding vessels were individually ligated and excised, and the mucosa was repaired with absorbable suture. Postoperatively the patient did well and at 60 months follow-up shows no recurrence.

Comment

Benign tumors of the esophagus are a small percentage of all tumors [1–3]. The patient's pathology showed recurrent schwannoma, a tumor composed of thin and plump spindle cells growing in fascicles and whorls with a distinct neuroid appearance (Fig 3). Occasional foci were hypercellular with nuclear polymorphism (Fig 4). Immunoperoxidase studies showed the tumor cells reactive for S100 but negative for keratin proteins and epithelium membrane antigen, supporting a nerve sheath origin of the tumor. The histology is extremely rare; few cases are presented in the world literature [4].

In these large lesions, peristalsis may aid in the development because of the loose submucosal tissue in the proximal esophagus.

These lesions can cause, proportional to the size of the polyp, small symptoms of mild dysphagia. Other symptoms included a mass in the throat and regurgitation of the polyp into the mouth with its disappearance on swallowing. Asphyxia, which can be fatal [5, 6], is due to the regurgitation of the polyp causing laryngeal airway obstruction. Malignant degeneration [7] is extremely rare.

Barium swallow shows a large, smooth, polypoid filling defect. Fluoroesophagogram often shows the defect is mobile with swallowing and esophageal contraction. Accurate diagnosis is best established, however, with endos-

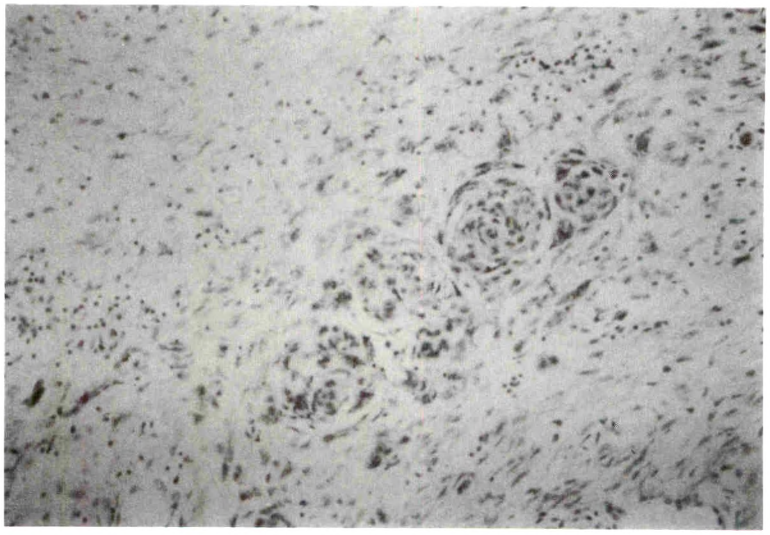

Fig 3. Photomicrograph showing characteristic pathology for a schwannoma, a tumor of thin and plump spindle cells growing in fascicles and whorls with a distinct neuroid appearance.

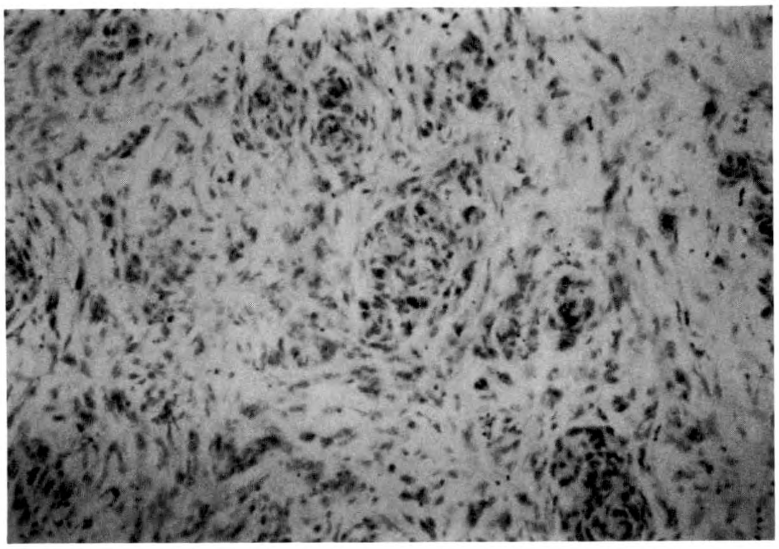

Fig 4. Photomicrograph of the schwannoma showing occasional foci that were hypercellular with nuclear polymorphism.

copy. A growth can be overlooked by the endoscopist, however, because of an intact mucous membrane over the intraluminal tumor and is often appreciated only by viewing the distal bulbous end of the polyp.

Endoscopic removal should only be attempted in selected patients with a relatively small tumor with a narrow stalk, as upper airway obstruction can occur. Such an acute situation is rectified by asking the patient to swallow. These large lesions often have high cervical attachments, which are quite vascular. Removal by diathermy snare may result in brisk, uncontrolled hemorrhage due to cervical vascular attachments.

Surgical removal is preferred, done through an esophagotomy where direct control of feeding vessels is easily accomplished. A thoractomy is rarely required. Excision of the polyp usually achieves complete relief of symptoms with relatively little morbidity. Occasional residual symptoms may be related to a severely dilated esophagus before operation.

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Vascularized Rib Strut Technique for Repair of Pectus Excavatum

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A vascularized rib strut based on the anterior intercostal branch of the internal mammary artery was applied to provide rigid internal fixation of the chest wall after correction of pectus excavatum. The procedure is simple and has substantial advantages when compared with techniques using metallic struts or nonvascularized free rib grafts.

(Ann Thorac Surg 1992;53:346–8)

The method described by Ravitch remains the most commonly performed procedure in the surgical correction of pectus excavatum [1]. Various devices for internal fixation have been used in an attempt to stabilize the chest wall postoperatively and to prevent recurrence of pectus excavatum. We have applied a vascularized rib strut based on the anterior intercostal branch of the internal mammary artery (IMA) to obtain chest wall stability. This is a new technique using a pedicled autologous bone strut that is assumed to be free from resorption and will provide permanent stabilization of a corrected pectus excavatum deformity.

Material and Methods

Anterior intercostal branches of the IMA pass laterally along the borders of the intercostal space to anastomose with the posterior intercostal arteries. Besides supplying the muscles and skin, they also supply the ribs through the periosteal vascular network. The vascularized rib flap can be raised based on the anterior intercostal branch of the IMA (Fig 1). When the distal side of the IMA is ligated and severed, the length of the pedicle makes it possible to reach anywhere in the anterior chest.

A vertical midline skin incision is made to obtain maximum exposure. A transverse inframammary incision may be used in young female patients. The procedure of correction of pectus excavatum deformity is basically a modification of Ravitch's technique. This includes subperichondral removal of all abnormal costal cartilages, supraxiphoid incision and manual mobilization of the substernal space, division of the intercostal bundles, oblique transection of the costal cartilage of the lowest normal rib, transverse anterior cuneiform sternal osteotomy, and tripod fixation of the sternum. We dissect the intercostal bundles medial to the IMA on one side to preserve the communication between the IMA and the anterior intercostal branches, and lateral to the IMA at the other side to maintain the circulation to the sternum (Fig 2).

After correction of the pectus excavatum deformity, the seventh rib (usually on the left side) is harvested as a vascularized rib strut. A 5-cm lateral chest incision just above and parallel to the seventh rib is made and the periosteum is exposed for a length of 15 cm. In the upper margin of the rib, the intercostal muscles are dissected, and then the space just anterior to the parietal pleura is divided bluntly to the next lower intercostal space. An intercostal muscle cuff of 5-mm width is attached to the lower margin of the rib to avoid injuring intercostal vessels. A flap is raised from the chest wall after the rib is cut posteriorly, and then the internal mammary vessels are severed distal to the bifurcation of the corresponding anterior intercostal branch. The rib strut is positioned under the distal portion of the mobilized sternum and is anchored bilaterally to the fifth ribs with wire sutures (Fig 3). Wire fixation of the sternum to the underlying strut is recommended. The incisions are closed in layers, with a suction drain tube placed behind the sternum.

Results

To date, we have treated pectus excavatum using this technique in 3 patients (a 26-year-old woman, a 24-year-

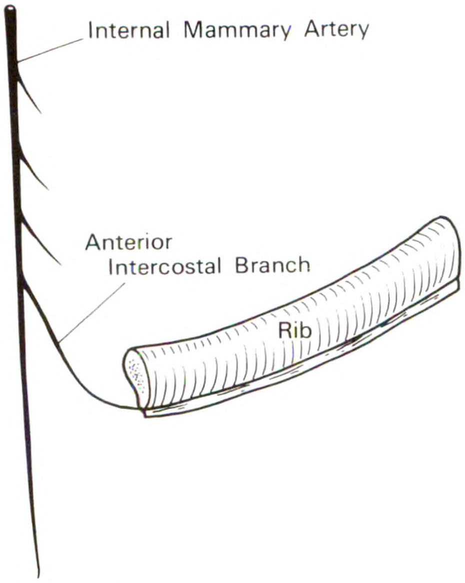

Fig 1. Vascularized rib strut based on the anterior intercostal branch of the internal mammary artery.

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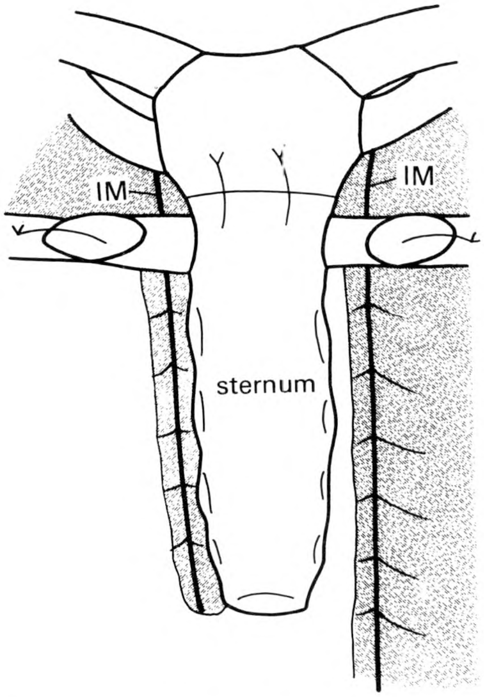


Fig 2. The corrected anterior chest wall after modified Ravitch's technique. (IM = *internal mammary artery.*)

old man, and a 6-year-old boy). Pneumothorax occurred perioperatively in the woman but was uneventfully cured through retention of a thoracic tube. Technetium bone scintigrams obtained 1 week after operation disclosed sufficient accumulation of the radioactive material in the transferred rib bone flaps. A chest computed tomographic scan obtained 2 years after operation demonstrated that the chest wall was satisfactorily fixed with the rib bone strut, as shown in Figure 4. During the follow-up period, ranging from 1 to 3 years, the deformity of the chest wall has recurred in none of the 3 patients.

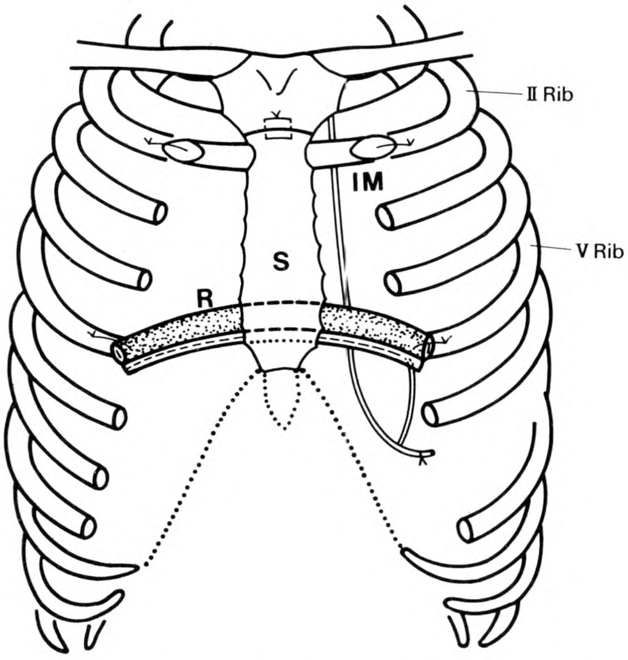
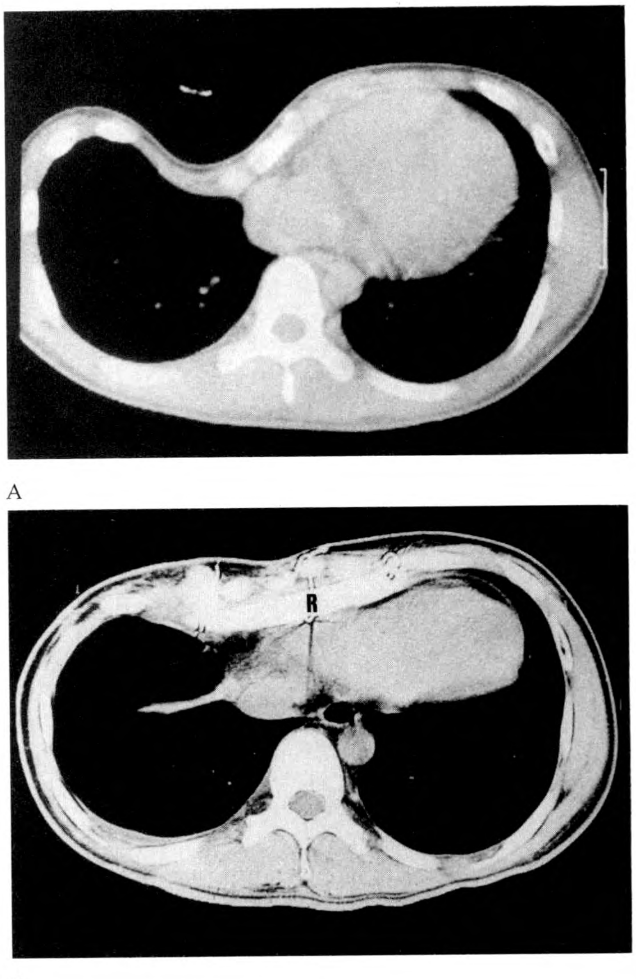


Fig 3. Internal fixation using a vascularized rib strut. (IM = *internal mammary artery;* R = *vascularized rib strut;* S = *sternum.*)


A

B

Fig 4. Computed tomogram of the chest before operation (A) and at 2-year follow-up (B). (R = *rib strut.*)

Comment

The currently preferred surgical management of pectus excavatum is a variation of the technique described by Ravitch in 1949. For teenagers and adults, however, internal fixation is necessary to stabilize the corrected anterior chest wall and obviate respiratory distress in the postoperative phase, as well as to prevent pectus excavatum recurrence. Many devices and materials have been reported to achieve this internal fixation. These include stainless steel struts [2], Kirschner wires or Steinmann pins [3], AO implants [4], and rib bone grafts [5]. Rigid fixation can be achieved using metallic materials; however, a common disadvantage of this technique is the necessity of a second operation to remove the strut.

Internal fixation using a vascularized rib strut has several advantages over the techniques described previously. Resorption of the rib is minimal, and early bony union will provide rigid fixation of the corrected chest wall. This method also has good applicability for children younger than 10 years of age because the vascularized rib is expected to grow, increasing its length. The rib flap reaches anywhere in the anterior chest, thanks to its long vascular pedicle. The operation can be done in a single stage, and stabilization of the chest wall permits the patient to ambulate early and resume normal activities shortly after operation.

It takes about 20 minutes to harvest a vascularized rib strut, and minimal blood loss is observed during the procedure. The loss of the seventh rib does not cause chest wall deformity or impair postoperative respiratory function, and the short scar on the lateral chest is quite acceptable. Pneumothorax is a possible complication of the procedure, so meticulous manual dissection of the pleura in all patients is important.

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Preoperative and Postoperative Hemopump Support for Patients Undergoing Orthotopic Heart Transplantation

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The Hemopump (Johnson & Johnson Interventional Systems, Rancho Cordova, CA) can be used successfully as a bridge to cardiac transplantation in patients with advanced cardiogenic shock that proves to be irreversible. Some patients, however, may also benefit from maintaining Hemopump support for a period of time after transplantation. A technique has been developed for continuing Hemopump support after transplantation that does not require repositioning of the device.

(Ann Thorac Surg 1992;53:349–50)

Patients in whom refractory cardiogenic shock develops while they are awaiting heart transplantation may be successfully managed with pretransplantation Hemopump (Johnson & Johnson Interventional Systems, Rancho Cordova, CA) left ventricular support [1, 2]. The Hemopump can also provide adequate end-organ perfusion in the event of poor postoperative cardiac function until the donor organ has recovered and is able to independently support the patient [3]. Allowing the Hemopump to remain in place through the perioperative period in this group of patients is desirable, because reexposing the insertion site and fluoroscopic repositioning of the device may be poorly tolerated. A technique is presented that allows for Hemopump support in patients having orthotopic cardiac transplantation and that does not require repositioning of the device.

Technique

With the Hemopump in place across the aortic valve [2], cardiac transplantation is begun in the usual fashion by performing a median sternotomy and opening the pericardium. An umbilical tape is passed around the aorta, and a 16F red rubber catheter is used to create a tourniquet. The aorta and vena cava are cannulated after systemic heparinization. Once total cardiopulmonary bypass has been established, the tourniquet is tightened, and the aorta is transected just superior to the coronary ostia. The Hemopump cannula is then removed from the ventricular apex, and a soft vascular clamp is placed across the non–wire-reinforced tip of the cannula to prevent backbleeding through the lumen of the pump. The clamp and cannula are then reflected out of the operative field for the remainder of the cardiectomy and implantation in which the atrial, pulmonary artery, and posterior aortic anastomoses are performed as usual (Fig 1).

Before completion of the anterior aortic anastomosis, the clamp across the Hemopump cannula is removed and the cannula tip is inserted, under direct visualization, through the aortic valve and into the ventricular apex. The anastomosis is completed, air is removed from the heart and aorta, and the aortic tourniquet is released. After Hemopump support has been reinitiated and cardiopulmonary bypass has been terminated, the wound is closed. The postoperative immunosuppressive regimen is individualized, depending on the type and degree of end-organ insufficiency in each patient.

Comment

The technique to continue Hemopump support after cardiac transplantation was applied successfully in a 42-year-old woman with dilated cardiomyopathy who, in her eighth month of pregnancy, experienced profound cardiogenic shock refractory to inotropic and intraaortic balloon pump support. Hemopump support was instituted by passing the catheter through the infrarenal aorta [2] because the patient's common femoral arteries were too small to cannulate. At the time of transplantation, the patient had hepatic dysfunction (serum bilirubin level, 308 μmol/L [18 mg/dL]) and severe coagulopathy, which prompted our decision to leave the Hemopump in place until adequate donor heart function and tolerance to immunosuppression had been demonstrated.

During the operation, no back-bleeding was noted from the Hemopump catheter under standard cardiopulmonary bypass perfusion pressures of 50 mm Hg to 60 mm Hg. The cannula was not damaged, and no repositioning of the catheter was necessary before initiation of Hemopump support. Flows from the Hemopump

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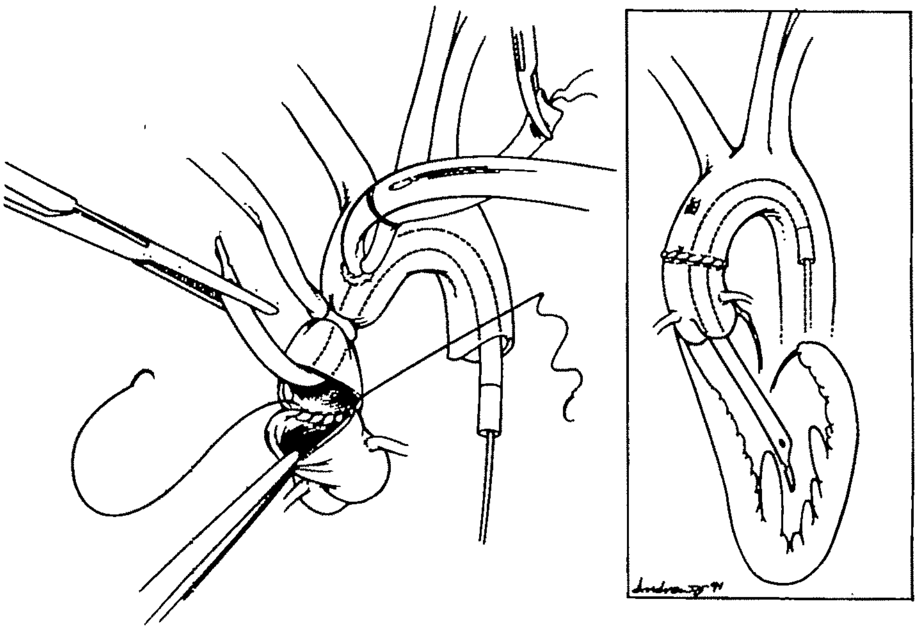

Fig 1. The aortic tourniquet prevents back-bleeding around the reinforced cannula, and a vascular clamp occludes the nonreinforced tip of the cannula.

were sufficient (3.0 to 3.5 L/min) to support the circulation until the donor heart attained satisfactory function. Delayed removal of the Hemopump on the third day after transplantation was well tolerated because of the short operative time, hemodynamic stabilization of the patient, and correction of the patient's coagulopathy.

We suggest using the technique of delayed Hemopump removal in patients being bridged to transplantation when simultaneous removal or repositioning of the device at the time of transplantation may risk additional morbidity.

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Rapid Transfusion After Aortic Decannulation

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A technique for rapid transfusion after aortic decannulation is presented. This technique facilitates the repair of the aortic cannulation site in difficult circumstances.

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Decannulation of fragile aorta after cardiopulmonary bypass may be associated with substantial blood loss, which can lead to hemodynamic instability. Time and effort may be required for repair of the bleeding cannulation site. For several years, we have been using a method of rapid transfusion after aortic decannulation, which is presented here.

Technique

After cardiopulmonary bypass is discontinued, the right atrial cannula is not removed but clamped and disconnected from the venous line (Fig 1). Similarly, the aortic cannula is clamped and disconnected from the arterial line. The arterial line is connected to the right atrial cannula and unclamped, and the system is ready for rapid transfusion (Fig 2). The patient is allowed to become mildly hypovolemic and hypotensive to facilitate repair of the aortic cannulation site with minimal tension on sutures. Only at this point is the aortic cannula removed and pursestring sutures are tied. Should bleeding occur, the blood is aspirated by pump suckers and returned to the right atrium while the surgeon is repairing the aorta. After the aortic cannulation site is secured, intravascular volume is repleted through the arterial line via the right atrial cannula. The right atrial cannula is then removed in the usual fashion, and protamine is administered.

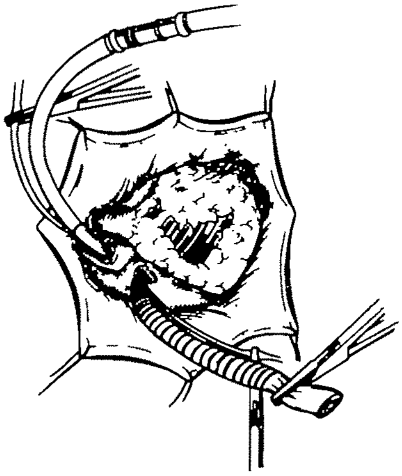

Fig 1. The venous cannula is clamped and detached from the right atrial venous line.

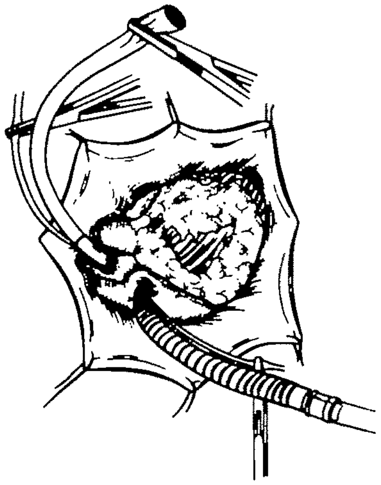

Fig 2. The arterial line is detached from the arterial cannula and, with evacuation of air, is attached to the venous cannula. This allows rapid transfusion of blood during or after repair of the aortic cannulation site.

Comment

A similar method of rapid transfusion during complicated aortic decannulation was proposed by Elami and coworkers [1]. In their method, the right atrium is decannulated first but the pursestring suture is not tied. Next, the aorta is decannulated and the aortic cannula is rapidly introduced into the right atrium and the tourniquet is tightened.

The distinct advantage of our method is that preparations for transfusion are made without removing the aortic cannula and without any haste. This allows both the surgeon and the first assistant to direct full attention to aortic decannulation and repair of the cannulation site. We have found this method to be simple and effective. It is routinely employed if there is any suggestion that repair of the aortic cannulation site may be difficult.

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Retrograde Cardioplegia: Current Methods

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Retrograde coronary sinus cardioplegia is being used for myocardial protection with ever-increasing frequency during complex cardiac operations. New methods for introducing cardioplegia into the coronary sinus have been facilitated by improved balloon-tipped catheters. Moreover, various solutions are being infused under both hypothermic and normothermic conditions with good results. This report provides background into the application of this technique and illustrates several methods for its daily use in clinical cardiac surgery.

(Ann Thorac Surg 1992;53:352–5)

In 1955, Lillehei first used retrograde coronary sinus perfusion for aortic valve operations. Over the past 15 years, however, antegrade cardioplegia has become the standard in myocardial protection for most cardiac operations. Now, because of the increasing complexity of valve and coronary operations, an interest in retrograde protection has been rekindled. Presently, 72% of cardiac surgeons in this country have used retrograde cardioplegia, compared with 91% who had never used the method in 1985 [1].

Technical Background

The coronary venous system resembles a sponge with multiple, axially arranged, interconnecting subepicardial tributaries penetrating all myocardial layers. Moreover, there is no indication that intramyocardial venous channels become affected by the atherosclerotic process. The use of retrograde coronary sinus cardioplegia is predicated on both of these features. When there is difficulty administering aortic root cardioplegia because of obstructed coronary arteries with poorly developed collaterals or aortic valvular insufficiency, retrograde coronary sinus cardioplegia may provide more uniform arrest and ideal cooling. Numerous laboratory and clinical studies have confirmed the efficacy and advantages of the retrograde method. Recently, combined antegrade and retrograde infusions have become popular as these methods provide quick arrest while maintaining uniform ventricular cooling [2]. Both crystalloid and blood-containing solutions have been shown to be effectively administered through the retrograde venous route, either as cold or warm infusions [3, 4].

With certain pathologic situations retrograde coronary sinus infusion potentially offers improved myocardial protection compared with antegrade cardioplegia, and may technically enhance complex cardiac operations. Currently, this method appears to offer *physiologic advantages* during coronary operations in patients with severe proximal multivessel coronary disease and with left main lesions. Retrograde cardioplegia has been beneficial during coronary reoperations in the presence of inadequate native coronary inflow, poor coronary collaterals, or a coexisting patent internal mammary artery graft, and in patients with a potential for atheromatous graft material embolization. Moreover, inadequate antegrade protection can occur during aortic valve operations in patients with

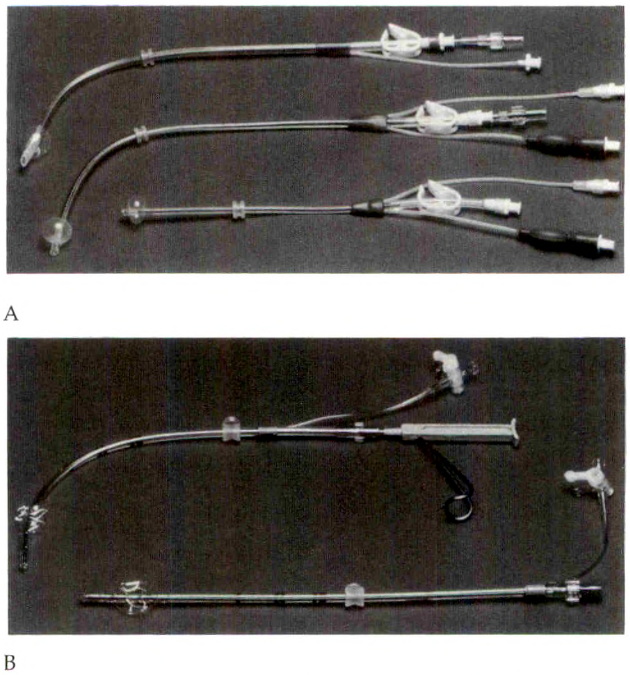

Fig 1. Retrograde catheters. (A) Top catheter has a flexible stylet and self-inflates with infusion of cardioplegia. Other catheters in this panel must be manually inflated. The small pediatric catheter requires an atriotomy and direct visualization of the sinus orifice for insertion. (B) Both of these catheters autoinflate with cardioplegia administration. The top catheter has a rigid, preshaped stylet with directing handle; the bottom has a flexible stylet. All catheters shown are commercially available.

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either coronary ostial stenosis or severe valvular insufficiency. In these patients, retrograde perfusion of protective solutions has been shown to be efficacious as well.

Retrograde cardioplegia has been advantageous to facilitate operations requiring lengthy arrest times and *maximum technical efficiency*. Procedures that may be facilitated by the technique include complex aortic root operations, with or without coronary reattachment (for example, the Bental procedure); aortic root enlargements; proximal ascending aortic dissections; pediatric cardiac operations in which rapid warming remains a problem and in which the administration of repeat antegrade cardioplegia is difficult (for example, the arterial switch operation); and either multiple or reoperative valve procedures. During mitral valve repair operations, air may be introduced into the aorta during retraction. For this reason our group has found retrograde cardioplegia preferable to multiple aortic root infusions. In valve operations requiring the addition of multiple coronary bypass grafts, the physiologic and technical advantages become additive. Although not clinically proven, the use of retrograde cardioplegia also may be very effective with hypertrophic ventricles and during cardiac transplantation, where intermittent administration of cardioplegia to donor hearts may be helpful.

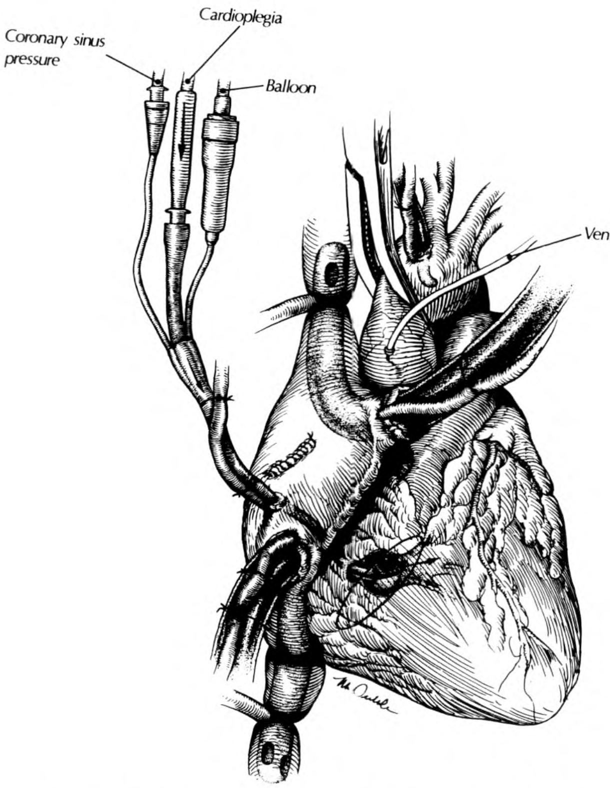

Fig 2. Direct coronary sinus cannulation for cardioplegia delivery. A small atriotomy is made in the mid-atrial wall and the aortic root is vented.

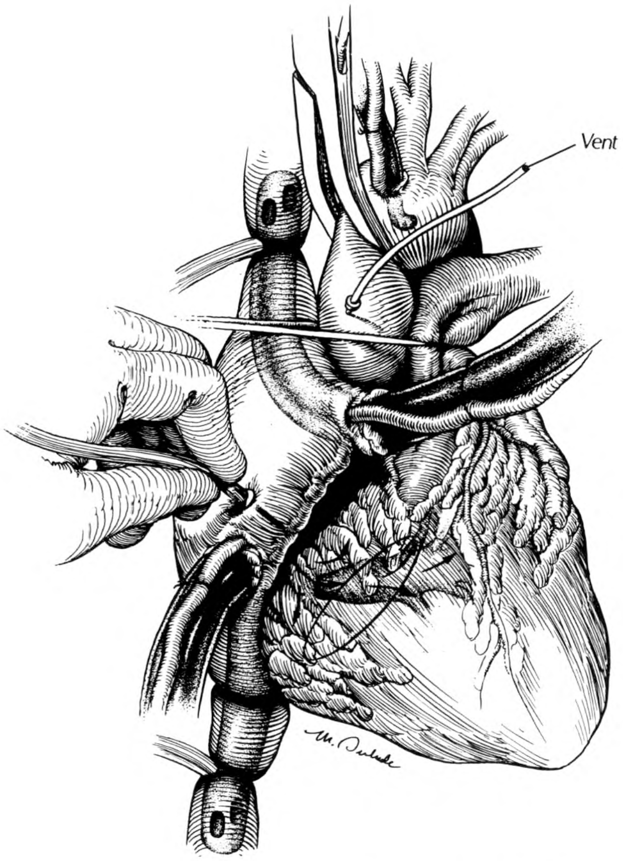

Fig 3. Cardioplegia is directly administered through the atrial wall. With bicaval and pulmonary artery occlusion, the cardioplegia is forced through the right atrium and ventricle into the coronary sinus orifice and thebesian channels.

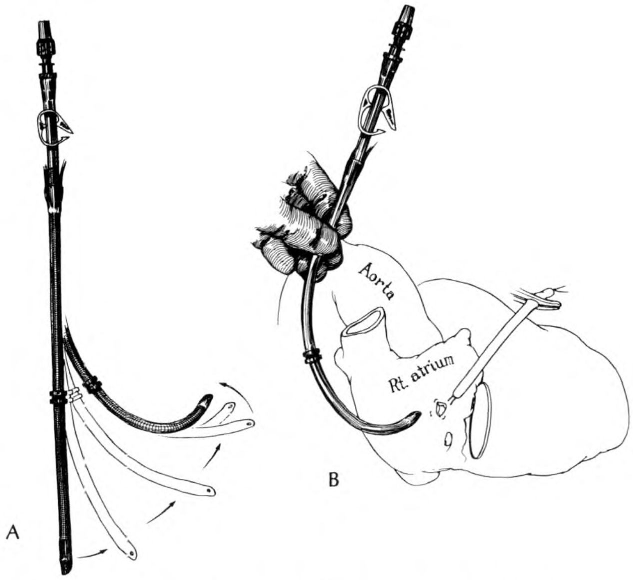

Fig 4. Transatrial intubation has become easier with the development of flexible stylet catheters. (A) The catheter is shaped in two planes and is directed forward and to the left hip. (B) A pursestring is placed in the anterior caudal atrial appendage before the venous drainage catheter is inserted. The catheter is introduced through the pursestring and atriotomy.

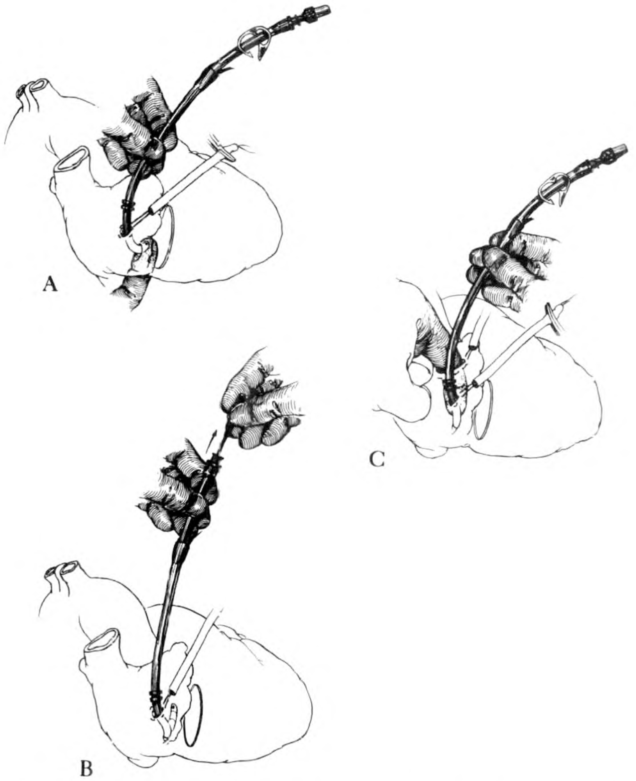

Fig 5. (A) The shaped catheter is held in the left hand with the right index finger palpating and directing the tip into the sinus orifice, located just anterior to the atriocaval junction. (B) The catheter is inserted several centimeters into the sinus while the stylet is carefully withdrawn. (C) An alternative method shows the right index finger placed through the venous return cannula site. This method may help direct difficult transatrial insertions that are complicated by a large sinus valve or small orifice.

Methods

Several catheters currently used for instituting retrograde cardioplegia are shown in Figure 1. Some require manual inflation of the coronary sinus balloon, whereas others autoinflate with infusion of cardioplegic solutions. During administration, the coronary sinus pressure should be measured and maintained at less than 50 mm Hg. Either intermittent or continuous infusions of cardioplegia may be administered by the retrograde route, with flow rates of 100 to 150 mL/min being optimal. When all cardioplegia is delivered through the sinus, arrest times appear to be slower than if solutions are given solely by the aortic root. Our group prefers to open the aorta or vent either the left ventricle or aortic root to allow the coronary effluent to escape. During retrograde administration, aortic venting seems important; however, the coronary venous system appears to provide adequate collateral outflow in the absence of suction venting. Some surgeons consider venting unnecessary and even deleterious, as it may prevent deep penetration of cardioplegia. Many surgeons use a septal thermistor to monitor intramyocardial temperatures, which helps determine the need for additional retrograde administrations. Although coronary sinus injury is infrequent, care must be used when inserting stiff stylet catheters.

A simple and very effective method for retrograde administration of cardioplegia is shown in Figure 2. Many surgeons adopt this open right atrial method for initial use of this technique. Moreover, this method is preferred when a tricuspid valve operation is planned or right atrial reoperative approaches to the mitral valve are selected. The inferior and superior venae cavae are cannulated directly or through the right atrium and caval occlusion is established. The coronary sinus catheter can be inserted under direct vision through a small transverse midatriotomy. Some authors recommend that the catheter not be advanced distal to the first venous branch, lest inadequate myocardial protection occur. However, our group has positioned the balloon tip several centimeters into the sinus to prevent intraoperative dislodgement and has achieved effective global myocardial cooling without right ventricular dysfunction. As shown in Figure 3, some surgeons administer the cardioplegic solution directly into the right atrium with occlusion of the pulmonary outflow tract. This method distends the right ventricle and atrium, driving the solution into the coronary sinus concomitantly. Although effective, this method has not been as popular as direct sinus cannulation.

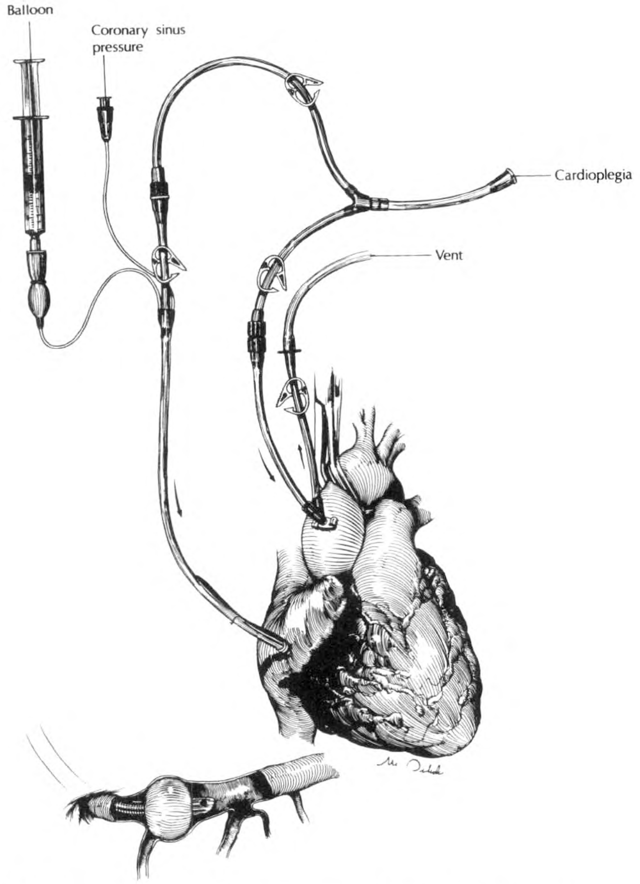

Fig 6. A method for alternately infusing antegrade and retrograde cardioplegia is shown. The aortic root should be vented during retrograde administration and the sinus balloon should be deflated during antegrade cardioplegia. The inset shows the final catheter position.

Newer cannulas allow blind, transatrial coronary sinus intubation, which is now the most commonly used retrograde method (81%). Gundry and associates [5] reported a large series of patients treated successfully by this method. For facile transatrial cannulation, the catheter/stylet can be shaped in two different planes (Fig 4A). The first bend gently curves the catheter anteriorly. The second curve should be sigmoid, directing the catheter tip to the left. A pursestring suture is placed in the mid-right atrium just below and a bit caudal to the atrial appendage (Fig 4B). It is easier to intubate the sinus when the catheter is positioned before the venous return cannula has been placed and cardiopulmonary bypass begun. However, hemodynamic or electrical instability may not afford this luxury. Moreover, dislodgement of the coronary sinus catheter is possible with the introduction of a venous return cannula, so this must be done with care. Position of the retrograde cardioplegia catheter should be reconfirmed after the venous cannula has been inserted.

Because of the larger profile, autoinflating balloons require a slightly larger atrial incision than manually inflated varieties. As shown in Figure 5A, the catheter should be held in the left hand and the tip introduced across the atrial wall. The right index finger is placed just medial to the right atriocaval junction, which is near the sinus orifice. The catheter tip is then directed toward the left iliac crest as the right index finger deflects the catheter into the sinus orifice (Fig 5B). After correct intubation, the catheter will be felt passing posteriorly along the atrioventricular groove in the coronary sinus. The catheter should be maintained within 3 cm of the orifice and the stylet carefully removed to avoid dislodgement (see Fig 5B). If a manual device is inflated, desaturated, pulsatile blood should reflux from the catheter. An alternative positioning method is to place the right index finger through the atrial appendage via the venous cannula pursestring with direct palpation of the sinus orifice (Fig 5C). This method is particularly helpful if a prominent coronary sinus (thebesian) valve makes insertion difficult by other methods.

The combined antegrade/retrograde approach has become increasingly popular. As shown in Figure 6, the initial dosage is administered through the aortic root to produce rapid arrest, and the retrograde cardioplegia is administered to maintain myocardial protection. Both warm and cold solutions may be administered intermittently or continuously using this approach. Usually, quick arrest is established with antegrade cardioplegia and retrograde sinus infusions are used thereafter.

Comment

Our group has found retrograde cardioplegia helpful technically and very protective during complex valve operations. To date, we have used the method in more than 75 patients who required arrest times exceeding 2 hours, with a single death. Although many issues regarding retrograde cardioplegia remained unsolved, this method represents a truly helpful modality for myocardial protection during most clinical situations. Ongoing cannula and perfusate research promise continued improvement and perhaps routine use by most cardiac surgeons.

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Cardiac Pheochromocytomas

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Cardiac pheochromocytomas are rare. Thirty cases have been reported in the literature. We report the cases of 2 more patients in whom the diagnosis was established using coronary angiography and who underwent surgical resection using cardiopulmonary bypass. We also review the literature on the subject.

(Ann Thorac Surg 1992;53:356–61)

Extraadrenal pheochromocytomas are rare. They are usually located in the abdomen. Thoracic pheochromocytomas constitute 1% to 2% of all cases of pheochromocytoma and are most often found in the posterior mediastinum. Cardiac pheochromocytomas are extremely rare, with only 30 cases reported in the literature [1–23]. Diagnosis and management of these tumors constitute a challenging problem to both the medical team and the surgical team. The purpose of this study is to report two additional cases of cardiac pheochromocytoma and to present a review of the literature on the subject.

Case Reports

Patient 1

A 26-year-old man was referred for resection of a cardiac pheochromocytoma. He was first seen at the age of 20 years because of bouts of arterial hypertension and headache. Two years later he was receiving β-blockers and was still hypertensive. Diagnostic workup revealed extremely elevated levels of blood and urinary catecholamines. Pheochromocytoma was suspected. Attempts to localize the tumor using iodine 131–labeled metaiodobenzylguanidine (I-MIBG) scintigraphy, computed tomography, and abdominal aortography failed. Antihypertensive drugs were again prescribed, and the patient was discharged.

Two years later he was readmitted for a hypertensive crisis and arrthymias. Blood and urinary catecholamine levels were still elevated, and total-body magnetic resonance images, computed tomographic (CT) scan, I-MIBG scintiscan, and abdominal aortogram were still negative. An exploratory laparotomy was performed, and no tumor was found. Six months later the patient was examined again. Total-body magnetic resonance images, CT scan, and I-MIBG scintiscan were again normal. Staged venous sampling showed a consistently higher level of catecholamines in the superior vena cava than in simultaneous venous samples from other sites. Coronary angiography showed a highly vascularized tumor on the posterior aspect of the heart. The blood supply of the tumor was derived from the left circumflex artery. The patient was referred for surgical intervention.

After adequate anesthetic preparation, a median sternotomy was performed and revealed a 4 × 3-cm reddish brown mass on the left atrial roof. Manipulation of this tumor resulted in arrhythmias and hypertension. Cardiopulmonary bypass was instituted, and the aorta was cross-clamped after cardioplegic arrest of the heart. The mass was then easily resected together with the underlying left atrial wall. An autologous pericardial patch was inserted to close the left atrium. The postoperative course was uneventful, and histological study showed the tumor to be an extraadrenal paraganglioma.

Two years later, the patient is normotensive and doing well without medication.

Patient 2

A 42-year-old woman was referred to our hospital for surgical treatment of a cardiac pheochromocytoma. She had a 10-year history of hypertension, was receiving antihypertensive therapy, and was considered to be in stable condition. In July 1989, she started complaining of

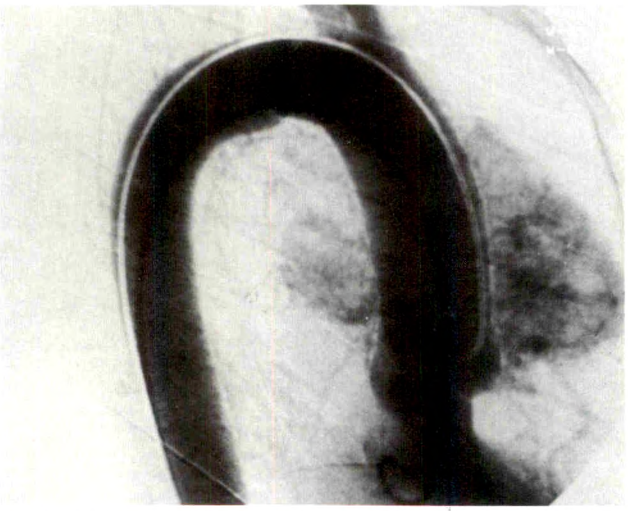

Fig 1. Aortogram showing the vascular blush on the anterior surface of the heart and behind the aorta.

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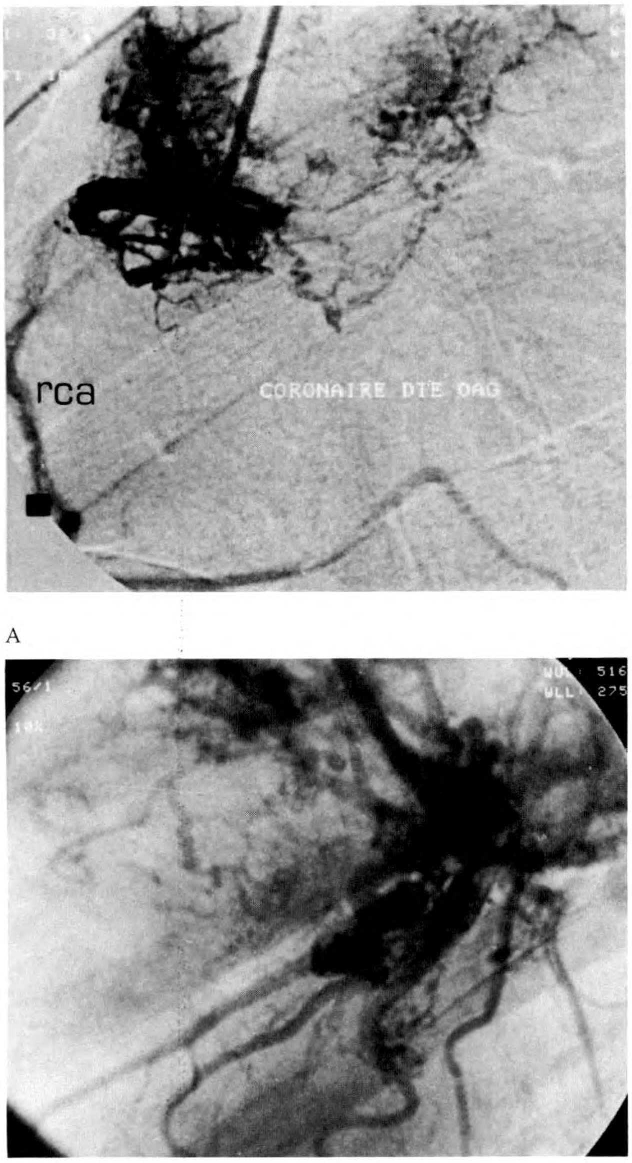

*Fig 2. Coronary angiography showed the blood supply of the tumor from (A) the right coronary artery (*rca*) and (B) the left main coronary artery.*

bouts of paroxysmal hypertension with episodes of palpitations and profuse perspiration. A complete workup was done and revealed markedly elevated levels of blood and urinary catecholamines. Pheochromocytoma was suspected. Abdominal CT scan showed a solid 2-cm mass in the left adrenal gland. Magnetic resonance imaging and I-MIBG scintigraphy did not confirm the typical aspect of pheochromocytoma. As no other localizations could be found, an exploratory laparotomy was performed and the mass resected. Pathological study indicated a nonsecreting adenoma of the adrenal gland. Postoperatively the patient continued to be hypertensive.

Two months after operation, the patient was readmitted for further studies. Abdominal and thoracic CT scans, magnetic resonance images, and I-MIBG scintiscan were all negative. Aortography and coronary angiography established the diagnosis by showing a highly vascular mass extending from the roof of the left atrium to the anterior surface of the heart (Fig 1). The blood supply of the tumor was derived from both the left main and right coronary arteries (Fig 2). The distal coronary vessels were normal. The patient was referred for surgical intervention.

After appropriate preoperative preparation with α- and β-blockers, a median sternotomy was performed. Incision of the pericardium revealed a large reddish brown tumor appended to the anterior wall of the right ventricle, originating from the aortic root and the pulmonary trunk and encompassing both vessels. The tumor extended posteriorly between the aorta and the pulmonary artery and adhered to the roof of the left atrium and to the right pulmonary artery (Fig 3).

Cardiopulmonary bypass was instituted between the femoral artery and both venae cavae. Manipulation of the tumor had no effect on blood pressure or cardiac rhythm. After cardioplegic arrest of the heart, the tumor was dissected sharply from the right ventricular wall. At the level of the aorta, subadventitial dissection of the tumor was undertaken. The first 2 cm of the right coronary artery was totally enveloped in the mass and had to be resected. Similarly, a 2 × 2-cm patch of the pulmonary artery was resected to completely liberate the mass anteriorly. Posteriorly, the tumor was sharply dissected from the left atrium and from the right pulmonary artery. The left main coronary artery was mobilized, and collateral vessels to the tumor were clipped. After total extirpation of the mass, a primary anastomosis between the right

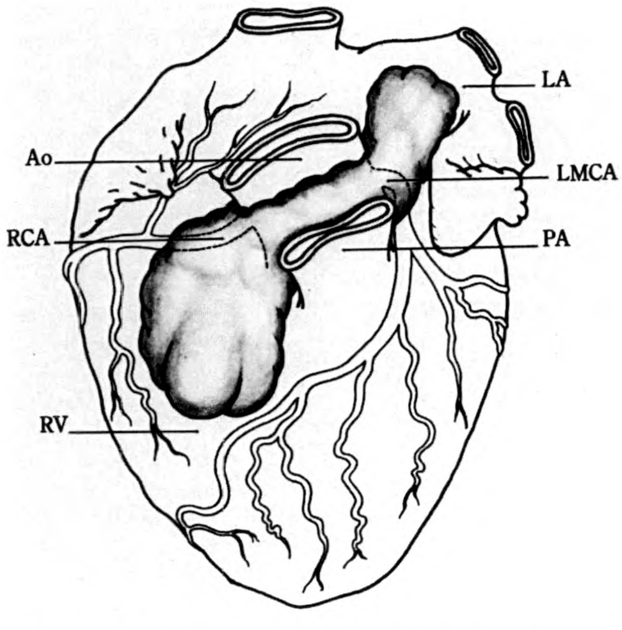

Fig 3. Exact localization of the tumor. (Ao = *aorta;* LA = *left atrium;* LMCA = *left main coronary artery;* PA = *pulmonary artery;* RCA = *right coronary artery;* RV = *right ventricle.)*

Table 1. Summary of Patient Data

Reference	Age	Sex	Clinical Presentation	Positive Diagnosis	Previous Operation	Other Locations
Joffre et al (1972) [1]	32	F	HT	Angiogram	Negative laparotomy	. . .
Besterman et al (1974) [2]	36	F	HT/labor	Angiogram	Negative laparotomy	. . .
Wilson et al (1974) [3]	32	M	HT	Staged venous sampling	2 Laparotomies, 1 negative	Right adrenal pheochromocytoma
Palubinskas et al (1980) [4]	49	M	NA	Staged venous sampling	3 negative laparotomies	. . .
Voci et al (1982) [5]	76	F	HT, CHF	Autopsy	. . .	Bone metastasis
Saad et al (1983) [6]	43	M	HT	I-MIBG	Negative laparotomy	. . .
Hodgson et al (1984) [7]	29	F	HT	Autopsy	Negative laparotomy	. . .
Shirkoda and Wallace (1984) [8]	42	M	HT	I-MIBG	Negative laparotomy	. . .
Shapiro et al (1984) [9]	NA	NA	NA	I-MIBG	2 Laparotomies, 1 negative	Bladder pheochromocytoma
. . .	NA	NA	NA	I-MIBG	. . .	. . .
. . .	NA	NA	NA	I-MIBG	2 Laparotomies, 1 negative	Abdominal paraaortic pheochromocytoma
. . .	59	F	HT, angina pectoris	Coronary angiography	. . .	Bone metastasis
Orringer et al (1985) [10]	24	F	HT	I-MIBG	Negative laparotomy, negative thoracotomy	. . .
. . .	18	F	HT/labor	I-MIBG	. . .	. . .
. . .	30	M	HT	I-MIBG	. . .	. . .
. . .	36	F	HT	I-MIBG	Negative laparotomy, positive thoracotomy	. . .
Awoke and Perlstein (1985) [11]	41	F	Headache, arrhythmias	I-MIBG	. . .	. . .
Cooley et al (1985) [12]	42	M	HT, arrhythmias	2-D echo, biopsy	Positive thoracotomy	Carotid body tumor
Fisher et al (1985) [13]	85	M	HT	I-MIBG	. . .	. . .
Geisler et al (1985) [14]	26	M	HT	Autopsy	Negative laparotomy	. . .
David et al (1986) [15]	35	F	Dyspnea, sweating	2-D echo, coronary angiography	. . .	. . .
Dunn et al (1986) [16]	48	M	HT	Staged venous sampling	Negative thoracotomy	Bil. carotid body tumors
. . .	38	M	HT	I-MIBG	2 Negative laparotomies	Carotid body tumor
Conti et al (1986) [17]	47	M	HT	I-MIBG	. . .	. . .
Shimoyama et al (1987) [18]	49	F	HT, headache	I-MIBG	. . .	. . .
Stowers et al (1987) [19]	28	F	Dyspnea, headache	Coronary angiography	. . .	. . .
Kawasuji et al (1989) [20]	46	M	HT, headache	2-D echo, I-MIBG	. . .	. . .
Lee et al (1990) [21]	31	F	HT	2-D echo	Negative laparotomy	. . .
Peiffert et al (1990) [22]	30	M	HT	Coronary angiography	. . .	Bil. carotid body tumors
Feltynowski et al (1990) [23]	40	M	HT	I-MIBG	. . .	. . .
Jebara et al (1991) present study	26	M	HT	Staged venous sampling	Negative laparotomy	. . .
. . .	42	F	HT, sweating	Coronary angiography	Negative laparotomy	. . .

Bil. = bilateral; CHF = congestive heart failure; HT = hypertension; I-MIBG = iodine 131–labeled metaiodobenzylguanidine; NA = not available; 2D = two-dimensional.

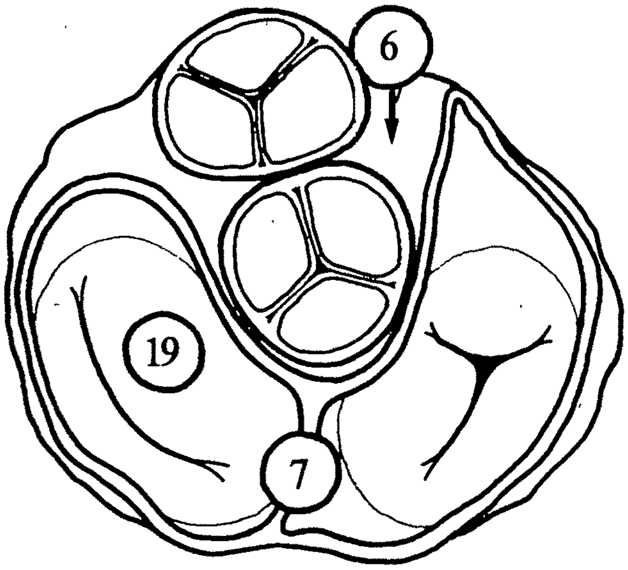

Fig 4. Sites of cardiac pheochromocytomas: left atrium (n = 19), interatrial septum (n = 7), and anterior surface of heart (n = 6).

coronary artery and the aorta was performed, and a 2 × 2-cm patch of autologous pericardium was inserted to close the pulmonary artery. At the completion of the operation, there was minimal bleeding from the tumor bed behind the aortic root, which was controlled with interrupted sutures and Surgicel (Johnson & Johnson, New Brunswick, NJ).

The postoperative course was marked by respiratory failure, which necessitated ventilatory support for 72 hours. The patient was discharged on the 18th postoperative day. She was normotensive with normal catecholamine levels. Histologically, the tumor was an extraadrenal pheochromocytoma.

Comment

Pheochromocytomas are functionally active chromaffin paragangliomas of the sympathetic nervous system. In adults, the majority of chromaffin cells are concentrated in the adrenal medulla, but small quantities can be found along the aorta, in the walls of blood vessels, and in the heart, prostate, and ovaries. These aberrant collections of chromaffin cells may constitute the site of ectopic pheochromocytomas. Pheochromocytomas secrete catecholamines and are usually responsible for arterial hypertension. They are encountered in less than 0.1% of all hypertensive patients [11, 21].

Ninety-eight percent of all pheochromocytomas are found in the abdomen. Less than 2% occur in the chest, usually in the posterior mediastinum [9, 10, 15, 23]. Cardiac pheochromocytomas are exceedingly rare. We were able to find 30 cases reported in the literature [1–23].

Table 1 shows a clinical summary of these 30 cases plus our 2 cases. There were 15 men and 14 women (sex not available for 3). Age ranged between 18 and 85 years (mean age, 40 years). The most common clinical presentation was arterial hypertension, usually associated with headache, palpitations, and sweating. At the time of diagnosis of the cardiac pheochromocytoma, clinical manifestations had been present for 2 months to 22 years. Two patients were seen because of a hypertensive crisis during labor [2, 10]. Three patients had undergone a previous resection of abdominal pheochromocytomas 22 years, 9 years, and 1 year previously [3, 9].

In all patients there were marked biochemical abnormalities that triggered the search for a pheochromocytoma. For no patient was there a family history of pheochromocytoma as is typically reported with chemodectomas, which are paragangliomas of the parasympathetic nervous system. Associated chemodectomas of the carotid body were found and resected in 5 patients [12, 16, 22]; two were bilateral.

The diagnosis of cardiac pheochromocytoma was consistently difficult to establish. In most instances, multiple locating procedures were performed in different combinations over several years before the site of the lesion was localized. Furthermore, during the diagnostic workup, negative exploratory laparotomy was performed in 17 of the 32 patients [1–4, 6–10, 14, 16, 21, present study], 2 of whom died postoperatively [7, 14].

The most useful study to establish the diagnosis of cardiac pheochromocytoma was I-MIBG scintigraphy. This technique resulted in localization of the tumor in 18 of the 22 patients in whom it was used. However, two I-MIBG scintiscans were obtained in each of our 2 patients and did not allow us to localize the pheochromocytoma.

Two-dimensional echocardiographic studies showed an abnormal cardiac or pericardial mass in 5 patients, thereby directing attention to the heart [12, 15, 20–22]. In these patients the diagnosis of cardiac pheochromocytoma was confirmed using I-MIBG scintigraphy in 3, coronary angiography in 1, and biopsy at thoracotomy in 1. Echocardiography was particularly helpful when the tumor was intracardiac.

In 7 other patients, the diagnosis of cardiac pheochromocytoma was established using coronary angiography [1, 2, 15, 19, 22]. This is a valuable procedure because it shows the exact location of the tumor as well as its relation to the coronary vessels. It also indicates the origin of the blood supply of the pheochromocytoma and thus helps in the planning of the surgical intervention.

Although a CT scan was performed in the majority of patients, this technique established the diagnosis in only 1 of them [18]. However, in every instance, after cardiac involvement was revealed using another technique, retrospective analysis of the CT scan showed the exact location of the tumor. The failure of conventional CT scanning to disclose the lesions may have resulted from failure to administer intravenous contrast medium, from slow infusion of contrast medium (during which time the tumor may enhance to the same degree as the cardiac chambers), or from failure to consider the middle mediastinum as a potential site for a pheochromocytoma [9].

Magnetic resonance imaging, with its superior soft-tissue contrast, appears to be a modality with great potential for diagnosing mediastinal masses [17, 24].

Table 2. Details of Surgical Intervention

Reference	Location	Incision	Cardiopulmonary Bypass	Technique	Outcome
Besterman et al (1974) [2]	LA roof	MS	Yes	Transection PA + AO	Cured
Wilson et al (1974) [3]	Interatrial septum	RT	No	. . .	Cured
Palubinskas et al (1980) [4]	Interatrial septum	RT	No	. . .	Cured
Saad et al (1983) [6]	LA roof, AO root	MS	Yes	. . .	Cured
Shirkoda and Wallace (1984) [8]	LA roof	RT	No	. . .	Cured
Shapiro et al (1984) [9]	Anterior surface of heart	MS	No	. . .	Cured
. . .	Interatrial septum	MS	Yes	. . .	Died (bleeding)
. . .	LA roof	MS	Yes	. . .	Not cured (metastasis)
Orringer et al (1985) [10]	LA roof	RT	No	. . .	Cured
. . .	Anterior surface of heart	MS	Yes	CABG	Cured
. . .	LA roof	RT	Yes	LA patch	Cured
. . .	LA roof	RT	Yes	LA patch	Died (bleeding)
Awoke and Perlstein (1985) [11]	Interatrial septum	MS	Yes	. . .	Died (bleeding)
Cooley et al (1985) [12]	LA roof	MS	Yes	Cardiac autotransplantation	Died (bleeding)
David et al (1986) [15]	LA roof	MS	Yes	Coronary sinus patch	Cured
Dunn et al (1986) [16]	Anterior surface of heart	MS	NA	. . .	Cured
Conti et al (1986) [17]	LA roof	MS	No	. . .	Cured
Shimoyama et al (1987) [18]	Anterior surface of heart	MS	Yes	. . .	Cured
Stowers et al (1987) [19]	LA roof	MS	Yes	Transection AO + PA, LA patch	Cured
Kawasuji et al (1989) [20]	Interatrial septum	MS	Yes	LA patch	Cured
Lee et al (1990) [21]	Interatrial septum	MS	Yes	Transection SVC, LA patch, CABG	Cured
Peiffert et al (1990) [22]	LA roof	MS	Yes	Transection AO, PA, SVC	Cured
Feltynowski et al (1990) [23]	Anterior surface of heart	MS	No	. . .	Cured
Jebara et al (1991) present study	LA roof	MS	Yes	LA patch	Cured
. . .	LA roof, anterior surface of heart	MS	Yes	PA patch, CABG	Cured

AO = aorta, aortic; CABG = coronary artery bypass grafting; LA = left atrial; MS = median sternotomy; NA = not available; PA = pulmonary artery; RT = right thoracotomy; SVC = superior vena cava.

However, at present, experience with the diagnosis of cardiac pheochromocytoma using this procedure is very limited. The several MRIs obtained in our 2 patients did not help us establish the diagnosis. However, as with the CT scans, retrospective analysis of the images allowed visualization of the cardiac tumor.

Staged venous sampling directed the diagnosis to the heart in 4 patients [3, 4, 16, present study] by showing a consistently higher level of catecholamines in the superior vena cava or its tributary veins compared with simultaneous venous samples obtained elsewhere.

In 3 patients the diagnosis of cardiac pheochromocytoma was established at postmortem examination [5, 7, 14]. Two of these patients died after a negative exploratory laparotomy, as mentioned previously.

With the advent of modern imaging techniques, cardiac pheochromocytomas will become an increasingly more frequently recognized cause of surgically correctable hypertension [10]. The fact that the majority of the 30 cases reviewed have been reported in the past 5 to 6 years supports this thesis.

Pheochromocytomas of the heart are most often found on the roof of the left atrium (n = 19). Other locations include the interatrial septum (n = 7) and the anterior surface of the heart (n = 6) (Fig 4).

Surgical excision of these tumors usually results in permanent cure and relief of symptoms. Operation was performed on 25 patients (Table 2). All underwent careful anesthetic preparation using α- or β-blockers or both before operation. Median sternotomy was performed in

19 patients and posterolateral thoracotomy in 6. In 6 patients, intraoperative manipulation of the tumor resulted in hemodynamic instability and arrhythmias.

Cardiopulmonary bypass was used in 17 patients. This technique permits total exclusion of the heart after aortic cross-clamping and cardioplegic arrest. The tumor can be excised without risk of hypertension or arrhythmias and with minimal blood loss. Furthermore, aortic cross-clamping allows safe dissection of the mass from the underlying myocardium and from the coronary vessels. It also allows the performance of coronary artery procedures to completely excise the mass, as was necessary in 4 patients [10, 19, 21, present study]. In our patient 2, 2 cm of the right coronary artery was resected, and direct reimplantation into the aorta was performed. In 8 patients, a segment of left atrial wall had to be resected with the tumor and was replaced by a pericardial or Dacron patch [10, 19–21, present study]. This was done in our patient 1, whereas in our patient 2, a segment of the pulmonary trunk was resected and replaced with a pericardial patch.

Some authors [2, 19, 21, 22] advocate transection of the great vessels to obtain direct access to pheochromocytomas of the roof of the left atrium. Even though the technique appears interesting and may offer technical advantages in certain instances, it did not seem necessary to our 2 patients. In 1985, Cooley and colleagues [12] described a new surgical approach to treat extensive tumors involving the posterior surface of the heart: cardiac autotransplantation after complete excision of the mass. We believe this technique deserves consideration in select patients with large invasive tumors.

Of the 25 patients who underwent surgical excision of the cardiac pheochromocytoma, 21 survived and 20 were reported to be completely cured. All four deaths were due to massive bleeding and occurred either intraoperatively or shortly after operation [9–12]. Nonlethal hemorragic complications were encountered in 4 other patients [2, 6, 19]. In fact, bleeding from the tumor bed (usually retroaortic) is the most common complication of this operation. In 1 patient, hypertension persisted postoperatively and was found to be associated with multiple skeletal metastases [9]. Malignant pheochromocytoma of the heart was encountered at the postmortem examination of another patient, a 76-year-old woman who died of chronic hypertension and heart failure and in whom generalized metastases were found [5].

We thank Patricia Retaggi for the preparation of the manuscript.

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ANNOUNCEMENT

1991 Meeting Southern Thoracic Surgical Association

The Thirty-eighth Annual Meeting of the Southern Thoracic Surgical Association was held at the Hyatt Regency Grand Cypress, Orlando, Florida, November 7–9, 1991. The President was Robert M. Sade, MD. Officers elected for the coming year are: *President*, William A. Cook, MD; *President-Elect*, Gordon F. Murray, MD; and *Vice President*, Joseph I. Miller, MD.

The following applicants were elected to membership:

David E. Allie, MD
Houma, LA

Carl Eric Anderson, MD
Greenville, SC

R. Mark Bodenhamer, MD
Oklahoma City, OK

John H. Calhoon, MD
San Antonio, TX

David V. Capallo, MD
Savannah, GA

David E. Carlson, MD
Abilene, TX

Richard A. Carlton, MD
Hickory, NC

William H. Coltharp, MD
Nashville, TN

Arthur J. Crumbley III, MD
Charleston, SC

Charles T. Everson, MD
Marrero, LA

T. Bruce Ferguson, Jr, MD
St. Louis, MO

Richard D. Floyd IV, MD
Lexington, KY

Edward B. Gerhardt, MD
Greensboro, NC

William C. Helton, MD
Raleigh, NC

Harold R. Howe, Jr, MD
Charlotte, NC

Charles E. Hunter, Jr, MD
Wilmington, NC

Julian E. Hurt, MD
Tallahassee, FL

Robert C. Jaggers, MD
Fort Smith, AR

Carl M. Johnson, MD
Paducah, KY

R. Michael Kennerly, MD
Fletcher, NC

L. Lee Lancaster, MD
Nashville, TN

Robert W. Linker III, MD
Louisville, KY

Gary K. Lofland, MD
Richmond, VA

Michael D. Maples, MD
Jackson, MS

Juan E. Martin, Jr, MD
Harlingen, TX

William H. Messerschmidt, MD
Johnson City, TN

Joel C. Morgan, MD
Winston-Salem, NC

Lawrence M. Nicholas, MD
Germantown, TN

Edmond W. Owen, Jr, MD
Memphis, TN

Anthony L. Picone, MD
Biloxi, MS

Joe B. Putnam, Jr, MD
Houston, TX

John G. Richardson, Jr, MD
Birmingham, AL

Carolyn E. Reed, MD
Charleston, SC

Harry M. Rosenblum, MD
Tallahassee, FL

F. Clark Sauls, MD
Alexandria, LA

Samuel L. Sehorn, MD
Houston, TX

Paul A. Spence, MD
Greenville, NC

Sergio Tavares, MD
Corpus Christi, TX

Ross M. Ungerleider, MD
Durham, NC

Raymond S. Waters, MD
Hudson, FL

J. Mark Williams, MD
Greenville, NC

Elevated to senior membership were: Safuh Attar, MD, Theodore L. Batchelder, MD, William D. Byrne, MD, Victor E. Cornett, MD, Hector Howard, MD, William C. Newman, MD, Daniel Nunn, MD, Takeshi Okano, MD, Michael G. Seremetis, MD, Daniel E. Smith, MD, and Norman B. Thompson, MD.

The President's Award for the best scientific paper given at the 1990 meeting was presented to Vincent Gott, MD, Reed Pyeritz, MD, Duke Cameron, MD, Peter Greene, MD, and Victor McKusick, MD, for their paper "Ascending Aortic Aneurysm in the Marfan Syndrome: Results of Composite Graft Repair in 100 Patients."

The 1992 meeting will be held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel (just north of Tampa), Florida, November 5–7, 1992. Chairman of the Program Committee will be Walter H. Merrill, MD, Chairman of the Postgraduate Committee will be Scott L. Faulkner, MD, and Chairman of the Membership Committee will be John P. Clarke, MD.

Hendrick B. Barner, MD
Secretary-Treasurer
Southern Thoracic Surgical Association
401 North Michigan Ave
Chicago, IL 60611-4267

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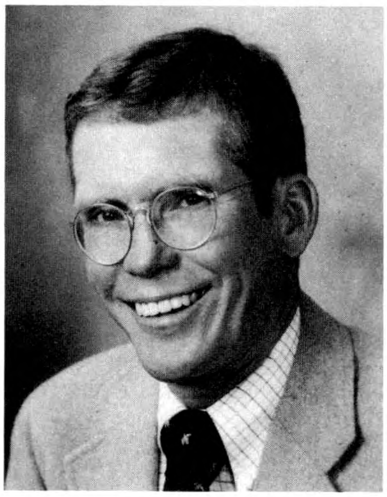
CORRESPONDENCE

Daniel A. Reid, MD: December 5, 1941–September 10, 1991



To the Editor:

Associates of Daniel A. Reid, MD, somberly report his death in a climbing accident on Mt Kenya, September 10, 1991.

Dr Reid and his wife, Barbara, were ascending Mt Kenya in Africa when they suddenly were swept off the mountain side by a rock avalanche, and both died instantly. Both were experienced mountain climbers, and Dr Reid was among five other Americans who were the first to reach the top of Mt Everest from the Tibetan side in 1983. His wife, Barbara, worked in support at the base camp.

Dr Reid received his thoracic surgery training at Albany Medical College from 1976 through 1978. He was certified by the Board of Thoracic Surgery in 1979 and recertified in 1991. Upon completing his training in Albany, NY, he started to practice thoracic surgery in Concord and Walnut Creek, CA.

His patients will recall his interest, empathy, kindness, and dedication. His colleagues will remember his "through the night" bedside attendance of critical postoperative patients.

Dr Reid's interests spanned beyond medicine. He was an avid runner, polo player, and advocate of physical fitness. In 1984 at the age of 44 he ran the grueling Western States 100-mile endurance run. To qualify for this race, 3 weeks prior to the event, he flew from California to Baffin Island to run a 50-mile course. He was a leader and participant in climbing expeditions to Patagonia, Alaska, and the Pacific Northwest, and had previously climbed in Africa. During the Vietnam war Dr Reid served three tours of duty where he earned his Green Beret and worked in the capacity of a physician equipping and operating field hospital units dedicated to the care of both military personnel and civilians. At a reception in his home following the successful 1983 Mt Everest expedition he gifted his treasured Green Beret to an astonished and pleased Sir Edmund Hillary.

His military career continued as a reservist until the present. He served with the 352nd Army Evacuation Hospital, Oakland, CA, with the rank of Lieutenant Colonel. He saw active duty for 4 months during the Persian Gulf call up.

Dr Reid is a recent applicant to The Society of Thoracic Surgeons and holds membership in The Western Thoracic Association, American College of Surgeons, and The American College of Chest Physicians. Dr Reid served on the board or was a member of a multitude and variety of organizations reflecting his diverse interests.

American Alpine Club
St. Andrew Society, San Francisco
Explorers Club
Diablo Valley Fly Fishermans Society
California Trout
Trout Unlimited
Sierra Club
United Polo Association
Nature Conservancy
Clan Donnachaidh Society
American Himalayan Foundation
Foundation for Glaciological & Environmental Research
Association United States Army
American Medical Joggers Association
Diablo Interpretative Society

Rolf G. Sommerhaug, MD
Steven F. Wolfe, MD
David E. Lindsey, MD

2700 Grant St, Suite 320
Concord, CA 94520

The Council of The Society of Thoracic Surgeons, at its meeting in Chicago on October 22, 1991, voted to recommend to the members of The Society the posthumous election to membership of Dr Daniel A. Reid. This action was taken in response to requests from many of his teachers and peers.

As a personal observation, I became acquainted with Dan and his wife, Barbara, during his years of general surgical education at the Virginia Mason Hospital. There is very little good in the loss of two such people. However, what there is, is contained in our remembrance of the sort of people they were, the values they held, the great good that they did in their lives, and, most of all, their inspiration which challenges us to be a little better, to try a little harder, and to do a little more than we think we can.

Richard P Anderson, MD

Secretary
The Society of Thoracic Surgeons

Bronchogenic Carcinoma With Chest Wall Invasion

To the Editor:

The recent article by Allen and associates [1] is an outstanding contribution to the literature on the operability for cure in bronchogenic carcinoma with chest wall invasion. The authors provide us with detailed information about how patients were selected, how those with mediastinal nodes were excluded, and how many operations were performed on all cases of lung cancer during this period. Although this report is much more detailed than many reports about "radical operation" in lung cancer, I wonder if some other information obtained from the Massachusetts General Hospital tumor registry would firm up the relative merits of chest wall resection as compared with symptomatic treatment: (1) Were the results of the 10 patients with rib destruction on plain chest roentgenograms as good as in the 42 patients without this finding? (2) How many patients with the same TMN staging were seen by a surgeon and refused resection during this period? We need to know the criteria for the refusals

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if we are to apply these data to our own patients. (3) How many patients were offered this procedure but refused for their own reasons? (4) How does the Kaplan-Meier plot look on the patients in groups 2 and 3?

Although this article—and several reports referenced in it—makes it clear that chest wall involvement is not an absolute contraindication for operation, I believe the addition of the above information would better define for the practitioner who should be considered for resective procedures. I would also humbly plead with the editors to request this information on all reports considered for publication, so that the mountains of data accumulated by tumor registries will not be for naught.

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Reference

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Reply

To the Editor:

My colleagues and I would like to thank Dr Aelony for his questions. They are indeed important questions and would add additional important information. Unfortunately, we have no way of retrieving information about which patients refused operation. This decision is usually made in the individual surgeon's office and not available. In addition, our TNM staging is a surgical staging. Comparison of a clinical TNM stage to a surgical TNM stage would be quite misleading. Our feeling about selection of patients can be stated simply: surgical resection should be considered if there is no sign of metastatic disease, the mediastinal nodes are negative by mediastinoscopy, and the patient has adequate pulmonary function to withstand the loss of the expected pulmonary tissue. We did not find any differences in survival related to depth of invasion of tumor. The 10 patients with rib destruction did just as well as those without rib destruction.

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Retrograde Cerebral Perfusion

To the Editor:

We read with interest a recent article by Crittenden and associates [1] entitled "Brain protection during circulatory arrest." As commented on by the authors, the reason retrograde infusion cerebroplegia did not yield a benefit and resulted in a poor outcome is unclear. In addition to their speculation, there is a prominent difference in the venous drainage system from the brain between humans and other mammals. In humans, the internal jugular veins are the major drainage vessels and they contain no functional valves. On the other hand, the external jugular veins are dominant vessels that have many functioning valves, and the internal jugular veins are rudimentary in mammals [2]. Those valves in the external jugular vein might obstruct retrograde infusion of cerebroplegia, causing the cerebroplegia to range over a restricted area, not the central nervous system.

Crittenden and associates speculated that diminishing of the transcerebral pressure led to accumulation of cerebroplegia. We wonder how cerebroplegia drained from the arterial system in their experiment. They did not mention that point in detail. We have clinical experience with continuous retrograde cerebral perfusion during systemic circulatory arrest for operations on the aortic arch. Continuous retrograde cerebral perfusion can be performed through the superior vena cava and the returned blood can be sucked from the opened aortic arch [3]. Clinical results were satisfactory, and the recovery of cerebral function in patients with continuous retrograde cerebral perfusion was better than in patients with conventional circulatory arrest. We expect that retrograde cerebroplegia in humans has cerebroprotective potential.

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Reply

To the Editor:

We appreciate the opportunity to reply to the letter of Ueda and Miki in which they question the methodology of retrograde perfusion in our study and detail their results [1] with clinical retrograde perfusion. As their letter indicates, the external jugular vein is the dominant vessel for venous return of both cranial and extracranial blood in rudimentary mammals. Inasmuch as any animal model is flawed with respect to its applicability to humans, we agree that this anatomic variation may be important. We do not believe that the venous valves provide a serious impediment to cerebral perfusion in our model for two reasons. First, we performed postmortem angiographic studies in 2 sheep. Contrast medium was injected in a retrograde fashion into the external jugular veins. We found that all of the cerebral vessels filled and drained into the aorta. Second, as noted in the manuscript, if the antegrade group is excluded, the nasopharyngeal temperatures for our retrograde group had the greatest diminution after the first hour of circulatory arrest. Thus, if nasopharyngeal temperatures are truly reflective of core brain temperatures, we believe that the cerebroplegic solution reached the target organ.

Our perfusion circuit had a reservoir connected to a venous line. Once the extracorporeal circulation had ceased, all of the animals were exsanguinated; therefore, blood from the venous circulation would fill the reservoir, usually within the first 5 to 10 minutes. The level in the reservoir would rise with the addition of dilute blood, commensurate with administration of cerebroplegia in the antegrade group. We did not observe this phenomenon in the retrograde group. We speculate that there was much more resistance to the efflux of retrograde cerebroplegia (carotid arteries to aortic arch to descending aorta to femoral artery to arterial line to impeller pump) into the arterial line. Although the jugular venous perfusion pressure was kept very low in the retrograde group, we suspect that the pressure in the brachiocephalic vessels was significantly greater than zero (unlike Ueda and associates' patients with an open aortic arch). For this reason we believe that the diminution in the transcerebral pressure gradient led to cerebral edema.

We would urge that the report by Ueda and associates be interpreted with caution. It is unclear whether their patients received barbituates before circulatory arrest or had external cranial cooling as is common practice in North America. The mean circulatory arrest time for their patients was only 35.6 minutes. This is well within the 45-minute time frame that has been shown to produce satisfactory results in similar patients without brain perfusion [2, 3]. What is more, Ueda and associates perfused the brain through the jugular vein with unadulterated pump blood. Unfortunately even in the absence of circulatory arrest, clinical and subclinical neurologic injury occurs with cardiopulmonary bypass [4, 5]. We believe that for true cerebroplegia to be established, the brain should be perfused with a solution that will preserve metabolic function of the brain and return the electrochemical processes of the brain back to baseline after a *protracted* period of circulatory arrest. More work is needed to achieve this end.

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Single Venous Cannulation for Valve Operations

To the Editor:

In a Letter to the Editor published in *The Annals of Thoracic Surgery* [1], Drs Balasundaram and Duran referred to a recently published article in which the authors were unaware that a technical innovation had been described 9 years earlier. Dr Balasundaram and associates [2] published an article concerning single venous cannulation for valve operations. I hasten to point out that this technical advance was first published in 1959 by Blanco and co-workers [3]. The original article described in great detail a major contribution to surgical technique, including clinical experience from 1957. The 1950s may appear prehistoric to a new generation of cardiac surgeons, but I am delighted to call attention to a scientific contribution made 31 years ago.

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Penetrating Injury of the Innominate Artery

To the Editor:

In the January 1991 issue of *The Annals*, McLean and McManus [1] presented a case of penetrating trauma involving the innominate artery. Reported experiences with this kind of vascular injury are very rare.

We reported a case of penetrating injury of the innominate artery in 1983 [2]. We had double-ligated this artery during operation but the vessel was found to be recanalized 1 year after operation. The innominate artery was then repaired by using an 8-mm Dacron tube graft interposed between the ascending aorta and the distal end of the innominate artery.

A 19-year-old man was brought to our emergency room in profound shock. He had been stabbed 2 hours before. The wound was in the sternal end of the left third intercostal space and extended to the right, beneath the sternum. Chest roentgenogram showed a large left hemothorax and marked widening of the superior mediastinum. Penetrating injury to one of the mediastinal arteries was suspected, and the patient was operated on immediately.

A median sternotomy was carried out. There was a large hematoma in the mediastinum. The innominate artery had partially been cut 1 cm above its origin. The active bleeding was controlled with digital compression, and because prolonged attempts to repair the laceration would jeopardize the patient's life, the innominate artery was ligated.

This procedure was tolerated well by the patient. There was no permanent neurologic deficit; however, right subclavian steal syndrome was present. Because of the long-standing postoperative wound infection, reconstructive intervention could not be done at this stage.

When the wound infection subsided the patient was discharged with the suggestion of a second operation for reconstruction of the innominate artery, which was necessary. The patient disappeared for a long period of time, however. One year later he showed up and he had no complaints. There were no limitations in his physical activity, even during exercise. Finding of the right radial and carotid pulses was surprising. Retrograde angio-

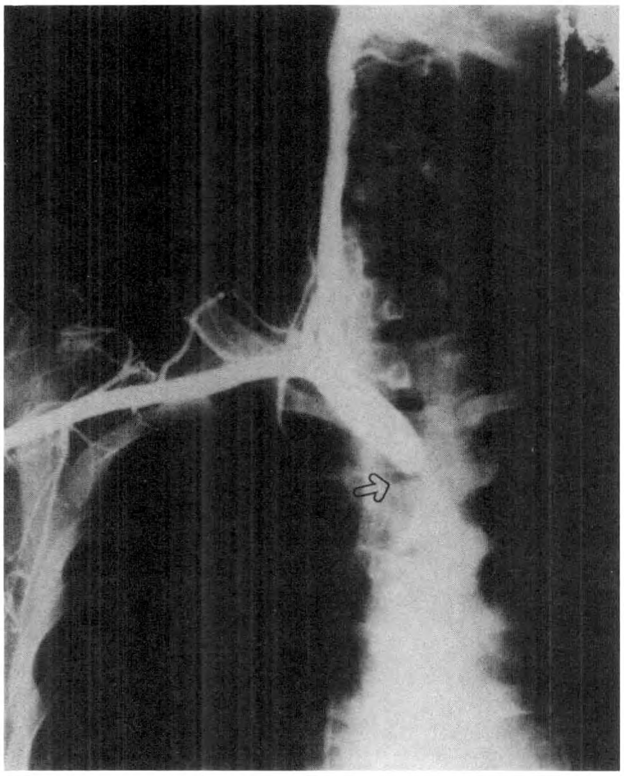

Fig 1. Angiogram shows recanalization of the ligated innominate artery (arrow).

graphic examination showed the recanalization of the ligated innominate artery (Fig 1).

In the second operation two silk sutures, used in the original ligation of the innominate artery, were found to have cut through the wall and lay within a small aneurysmal sac. This part of the innominate artery was excised, and the origin of the innominate artery at the aorta was sutured. An 8-mm Dacron prosthesis was interposed between the ascending aorta and the distal end of the innominate artery.

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Retrograde Continuous Warm Blood Cardioplegia

To the Editor:

I read with interest the report from Salerno and associates [1] on the technique and pitfalls of retrograde continuous warm blood cardioplegia. After verbal reports from members of the group at St. Michael's Hospital in Toronto, our group began using continuous warm blood cardioplegia in the spring of 1990 and have become quite comfortable with the technique.

Having performed close to 200 open heart cases with this new form of myocardial protection, I reviewed the last 100 cases of nonredo, isolated aortocoronary bypass grafting done using cold intermittent blood cardioplegia, as well as 100 cases of warm continuous retrograde blood cardioplegia. Comparison studies showed no significant difference in the surgical outcome of these two groups, as indicated in Table 1.

All deaths involved male patients, age 62 and 60 years in the warm cardioplegia group and 66 years in the cold cardioplegia group. The first patient died 19 days postoperatively of a sudden pulmonary embolus, after an initially difficult time due to chronic obstructive pulmonary disease that required 5 days on ventilatory support. The second underwent uneventful triple aortocoronary bypass grafting; after an initially stable postoperative period, the patient became hypotensive with low cardiac output that could not be reversed, and the patient died in a low cardiac output state due to ischemic cardiomyopathy. At the autopsy all grafts were found to be patent and no localized infarct was seen; extensive myocardial fibrosis and generalized ischemic myocardium were found. The last patient died late. Having undergone a laparotomy for control of gastrointestinal bleeding, the patient suffered a pulmonary embolus the day after discharge from the hospital.

Although there was no major difference in the outcome of these two small groups of patients, we have been very pleased with the degree of myocardial protection provided by the use of continuous warm blood cardioplegia, particularly with the retrograde infusion. It appears to provide good ventricular myocardial distribution and does not necessitate the use of multiple lines and cannulas attached to the newly placed grafts, which is particularly advantageous for those of us who do distal anastomoses first.

I should note, however, that during the initial phases of adaptation to this technique we noticed an unusual number of patients with postoperative atrial fibrillation and, although we did not document this problem in numbers, this impression was shared by all four cardiac surgeons. At the time, we were using continuous cardioplegia flows between 50 and 150 mL/min and could see the presence of persistent P waves on the electrocardiographic monitor throughout the period of ventricular arrest.

Table 1. Comparison of the Two Groups

Variable	Warm Continuous Blood Cardioplegia	Cold Intermittent Blood Cardioplegia	*p* Value
No. of Patients	100	100	NS
Male/female	84/16	80/20	NS
Average no. of grafts	3.4	3.43	NS
Av. ischemic time per graft	15 min 21 s	14 min 10 s	<0.01
Average age (y)	59.96	62.68	<0.025
Operation			
Elective	25	23	NS
Urgent	67	74	NS
Emergency	8	2	NS
Intraaortic balloon pump	3 (1 preop)	4 (1 preop)	NS
Deaths	2	1	NS
Atrial fibrillation	7	5	NS

NS = not significant.

Since then we have been using much greater perfusion volumes, as high as 300 mL/min in normal-sized hearts and greater volumes in hypertrophic hearts as long as the perfusion pressure measured at the tip of the coronary sinus cannula is less than 40 to 45 mm Hg. We still see persistent P waves in the electrocardiographic monitor, as a sign of inadequate potassium distribution to the atria, but are seeing a lower incidence of postoperative atrial fibrillation, although we continue to use low-dose propranolol as prophylaxis for this problem.

Salerno and associates reported that cardioplegia delivery should not exceed 250 mL/min, and I wonder at their rationale for doing so. I am also interested in knowing the incidence of atrial fibrillation in their group of patients, particularly in those undergoing isolated coronary artery bypass grafting and with no previous atrial fibrillation.

Interestingly, we have not found any problems with hyperkalemia postoperatively, and hypokalemia has also been a very infrequent problem, necessitating far less postoperative intervention with electrolyte replenishment. This has been a welcome relief, as these normothermic patients tend to have a smoother postoperative phase, no longer needing to recover from the hypothermic phase.

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Reference

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Reply

To the Editor:

Retrograde continuous normothermic blood cardioplegia (RCNBC) has been well received among cardiac surgeons, although my colleagues and I await clinical trials to prove its value compared with conventional techniques of myocardial protection. The idea of prevention of ischemia during heart operations is appealing, and RCNBC appears to allow the surgeon to achieve this goal. The results reported by Dr Aldrete are encouraging and indicate that RCNBC is at least comparable with intermittent cold blood cardioplegia.

Not mentioned in Dr Aldrete's letter, but implied, is that these patients were systemically perfused at normothermia (37°C). As mentioned, the technique of RCNBC is simple for surgeons who are already using intermittent cold cardioplegia through the retrograde route. For those not using the retrograde method there will be a learning curve, which has been made easier by the development of appropriate cannulas such as that developed by Drinkwater and associates and its modification (normoplegia cannula, Research Medical, Salt Lake City, UT). The technique relies on perfect placement of the cannula in the coronary sinus and monitoring of its position by pressure and, more recently, by intramyocardial oxygen tension (oxygen tension probe; Innerspace, Irvine, CA).

Dr Aldrete suggests that P wave activity during RCNBC may reflect the adequacy of cardioplegic flow in the coronary sinus. This remains to be proved. At this point the relationship between coronary sinus cardioplegic flow and atrial activity/inactivity during aortic clamping and fibrillation after declamping remain undefined. The rationale for the use of a specific flow during RCNBC is intuitive, and the recommendation of a pressure of 40 mm Hg of RCNBC is based on cold blood cardioplegia delivery, which may not be applicable for RCNBC. We have observed higher flows at 40 mm Hg infusion pressure compared with cold techniques. How much flow is ideal for the hypertrophied heart or the ischemic heart will have to be determined in further clinical studies. We believe that the hypertrophied heart should received higher flows compared with normal hearts.

As observed by Dr Aldrete, hyperkalemia is rarely a problem, even in patients in renal failure. When the systemic level of potassium becomes a concern, the surgeon has the option of discontinuing potassium in the cardioplegia, simply delivering warm blood, as we routinely now do for prevention of hyperkalemia or when we are constructing the last distal anastomosis and before declamping. We also believe that the postoperative course of patients receiving normothermic cardioplegia and normothermic perfusion is usually uncomplicated. Although Dr Aldrete's series of patients had normal hearts, RCNBC is particularly suitable for valvular repair, high-risk patients such as those with acute events, multiple procedures, or hypertrophied ventricles.

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Internal Mammary Artery Preparation

To The Editor:

Prompted by the recent report from John and associates [1], I describe my technique for harvesting the internal mammary artery (IMA) which, although also based on the principle of hydrostatic pressure, differs in several important details.

After sternotomy, an IMA retractor (eg, Rultract) is used to elevate the sternal edge and the pleura is opened along the full length of the IMA with electrocautery. Two milliliters (60 mg) of papaverine HCl (Lilly, Indianapolis, IN), diluted to 30 mL, is shaken with air in a 50-mL Luer-Lok syringe to produce a foamy mixture, which is then forcibly injected along the course of the IMA, beginning inferiorly (Fig 1). An olive-tipped needle (Fig 2) is used to avoid injury to the IMA. This is repeated once if necessary until the tissue containing the pedicle becomes boggy. This allows for easy separation of the pedicle from the overlying bone and cartilage.

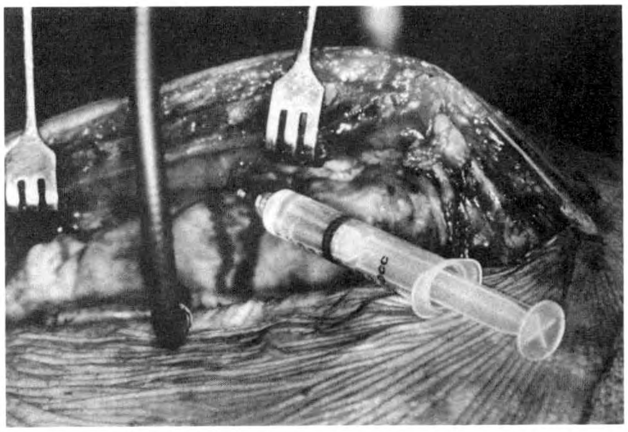

Fig 1. Papaverine solution is injected along the course of the internal mammary artery.

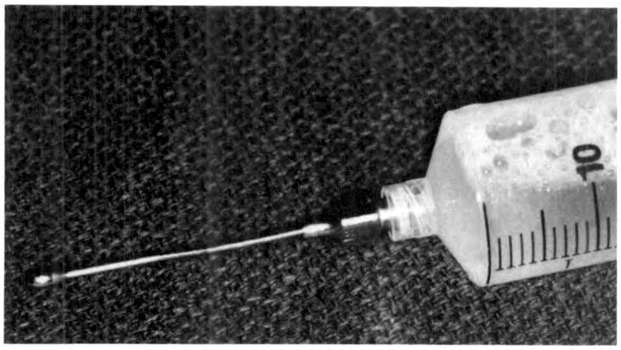

Fig 2. The olive-tipped needle used to avoid injury to the internal mammary artery.

The IMA pedicle is then harvested using standard techniques with electrocautery set at 40 coagulation. The knife blade is covered, save for the distal 3 mm, with a segment of 8F red rubber feeding tube to avoid heat transfer. All branches are cauterized, but large ones may be clipped. The IMA is taken as far cephalad as possible, so that it falls medial to the lung. This avoids traction by the inflating lung, even in cases of emphysema. The IMA is divided distally between large Ligaclips (Ethicon, Somerville, NJ) at or beyond the bifurcation, depending on desired length. The pedicle is checked for bleeders and is tucked into the pleural cavity until ready for use. The blood pressure is maintained between 110 and 130 mm Hg. This will enhance further dilation of the papaverine-logged IMA as it pulsates against the Ligaclip.

My colleagues and I have employed this technique with success in more than 300 cases. It is safe and rapid (10 to 20 minutes) and is particularly advantageous for bilateral IMA harvest. This technique avoids the need for intraluminal instrumentation and injection of the IMA, which, although producing a large bounding IMA on the table, have resulted in the so-called string sign in several patients and are no longer used by our service.

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Emergency: An Urgent Problem Emergent?

To the Editor:

In an era in which statistics and significance are considered crucial to scientific writing, I am alarmed to see the word *emergent* [1], used freely in American hospitals, now acceptable in print.

What does this word mean? The Oxford English dictionary [2] described emergent both as being used *improperly* for "urgent" or pressing and an *obsolete* usage meaning "emergency."

Interestingly, the word in a scientific sense is the opposite of resultant, and defines an effect produced by a combination of several causes, but not capable of being regarded as a sum of their individual effects [2].

Is there a standard for defining urgent and emergency as they determine the timing of surgical (and other) interventions? If there is no such rule, may I suggest that the editors of major surgical publications agree on a usage that is unambiguous.

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References

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Editor's Reply

Dr Hoffman's letter raises several interesting points. As a journal editor, I, too, have wondered about the use of the word *emergent* in this context. But the shades of meaning in words depend on two things: their usage in the spoken language and who writes them down. Most of the abridged dictionaries define *emergent* only as the adjective form of the verb *emerge,* which itself means to rise out of or come forth from an enveloping fluid, hence, to come into view. The unabridged editions list *emergent* as a separate word and give additional definitions. Random House, for instance, has three listings that relate to emerge, and then adds two others, "4. arising casually or unexpectedly. 5. calling for immediate action: urgent."

The words *emerge, emergence, emergency,* and *emergent* all have the same root derivation [L. e, out; *mergere,* to plunge]. Looking at it logically, one might more appropriately question how the word *emergency* (and sometimes its minor deviant, *emergent*) became the maverick in the family. This question has been referred to the best authority this editor knows, Mr William Safire, the columnist writing "On Language" for the *New York Sunday Times.*

Used as adjectives in a medical context, *emergent* and *emergency* seem to convey the same need for immediate action by the physician, and therefore are useful words. My sense is that both carry a higher priority in this regard than does the word *urgent.* As for Dr Hoffman's request that editors agree on unambiguous timing definitions for these terms, I applaud the idea, but despair for the outcome.

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ American College of Surgeons, Orlando, Florida—March 22–25, 1992

For information on this meeting, contact American College of Surgeons, 55 Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

■ General Thoracic Surgery, Las Vegas, Nevada—April 2–3, 1992

This postgraduate course is sponsored by the American College of Chest Physicians and the University of Nevada School of Medicine. For information, contact ACCP, Division of Education, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Twelfth Annual Meeting of the International Society for Heart Transplantation, San Diego, California—April 2–4, 1992

For information on this meeting, contact ISHT, 435 N Michigan Ave, Suite 1717, Chicago, IL 60611; or telephone (312) 644-0828.

■ One Hundred Twelfth Annual Meeting of the American Surgical Association, Palm Desert, California—April 6–8, 1992

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Forty-first Annual Meeting of the American College of Cardiology, Dallas, Texas—April 12–16, 1992

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ Seventy-second Annual Meeting of the American Association for Thoracic Surgery, Los Angeles, California—April 27–29, 1992

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Thirty-eighth Annual Meeting of the American Society for Artificial Internal Organs, Nashville, Tennessee—May 7–9, 1992

For information on this meeting, contact ASAIO Registration, 2200 North Federal Highway, Suite 201, Boca Raton, FL 33431-7710.

■ Fourteenth World Congress of The International Society for Heart Research, Kobe, Japan—May 10–14, 1992

For information on this meeting, contact Makoto Nagano, MD, Secretariat, XIV World Congress of ISHR, Department of Internal Medicine, Jikei University Medical School, Aoto Hospital, 6-41-2 Aoto, Katsushika-ku, Tokyo 125, Japan.

■ The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Chicago, Illinois—June 8–10, 1992

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Cardiostim 92, Nice, France—June 17–20, 1992

For information on this meeting, contact Dr J. Mugica, Centre Chirurgical Val d'Or, 16, rue Pasteur, 92211 St-Cloud Cedex, France; or telephone (33) 1.46.02.70.72 (facsimile: (33) 1.46.02.05.09).

■ Eighteenth Annual Meeting of The Western Thoracic Surgical Association, Kauai, Hawaii—June 25–27, 1992

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Forty-first International Congress of the European Society for Cardiovascular Surgery, Montpellier, France—September 6–9, 1992

For information on this meeting, contact ESCVS Congress 92, Le Corum, BP 2200-F 34027, Montpellier Cedex 1, France; or telephone (33) 67.61.67.61 (facsimile: (33) 67.61.67.00).

■ Sixth Annual Meeting of The European Association for Cardio-Thoracic Surgery, Geneva, Switzerland—September 14–16, 1992

For information on this meeting, contact Symporg S.A., 108, route de-Frontenex, CH-1208 Geneva, Switzerland; or telephone 41-22 786 37 44 (facsimile: 41-22 786 40 80).

■ First International Meeting of Thoracic Surgery, Barcelona, Spain—October 9–10, 1992

For information on this meeting, contact Congress Secretariat, RCT asociados, Aulèstia i Pijoan, 12, 08012 Barcelona, Spain; or telephone 34-3-4156938 (facsimile: 34-3-4156904).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 26–30, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

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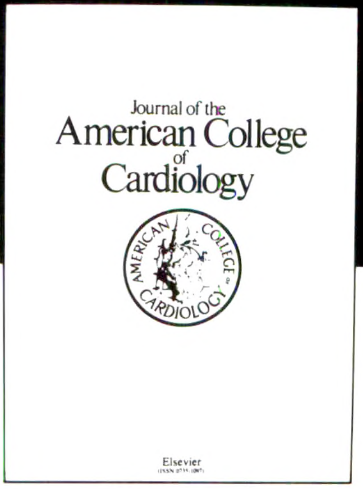
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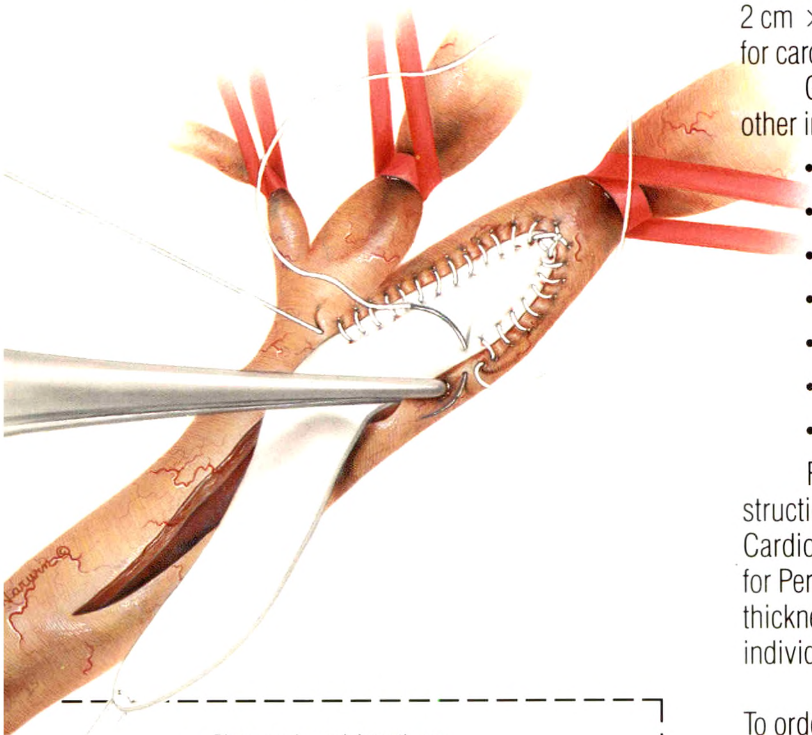

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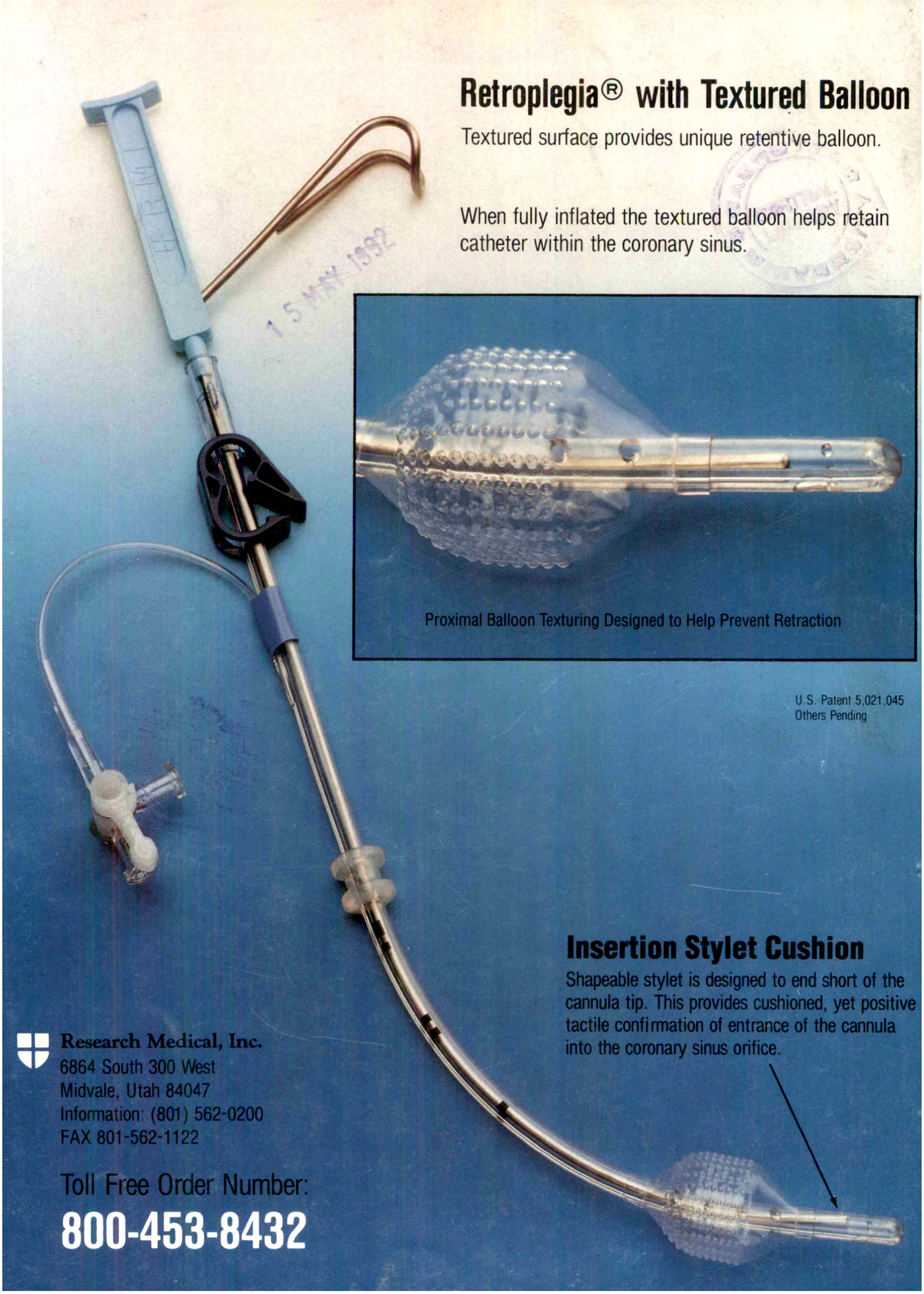

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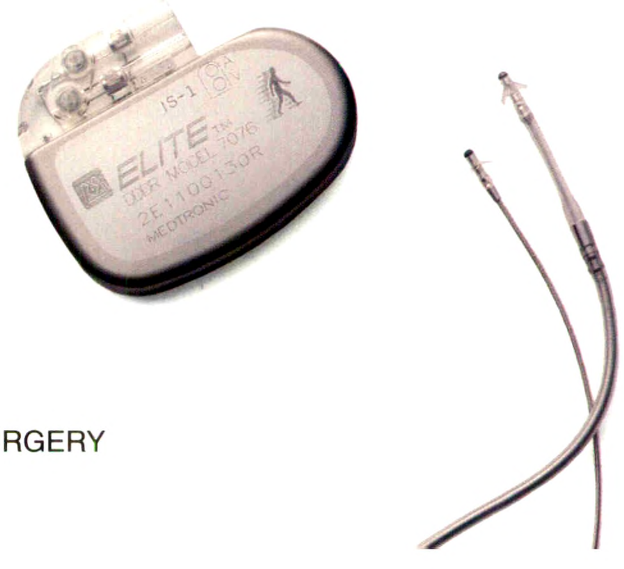

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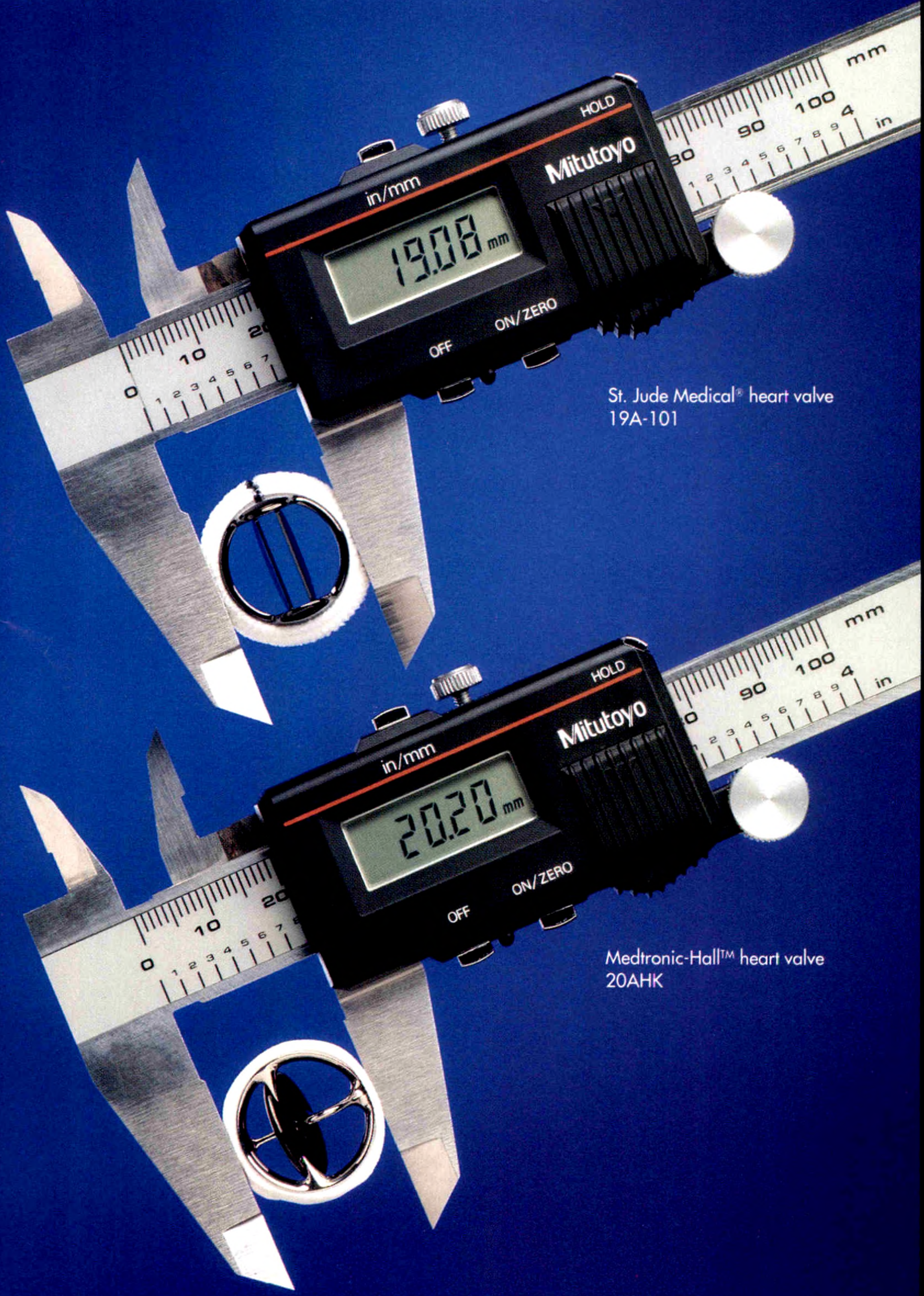

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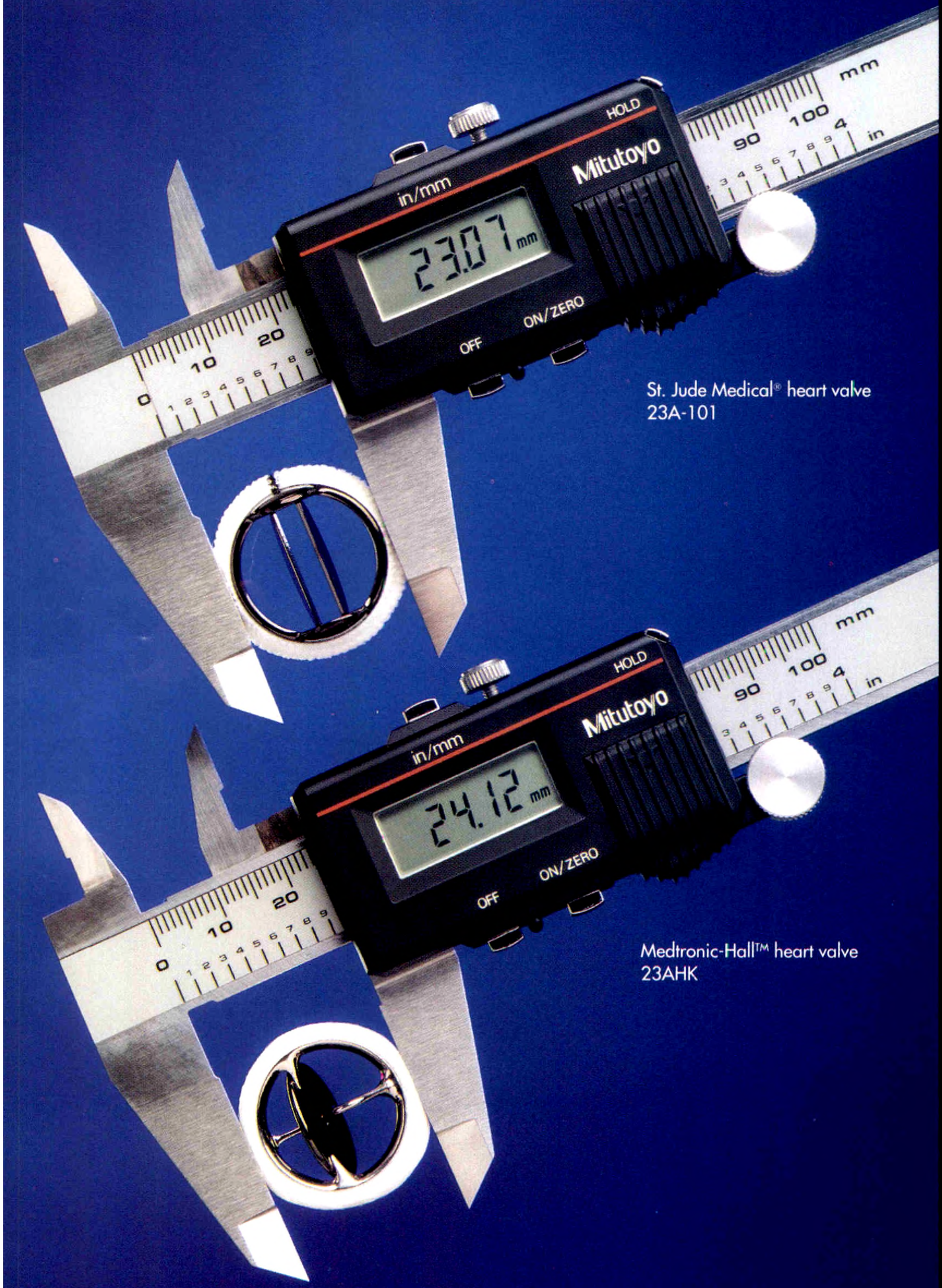

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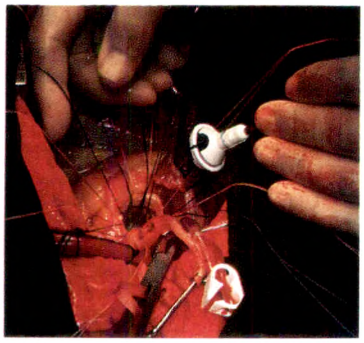

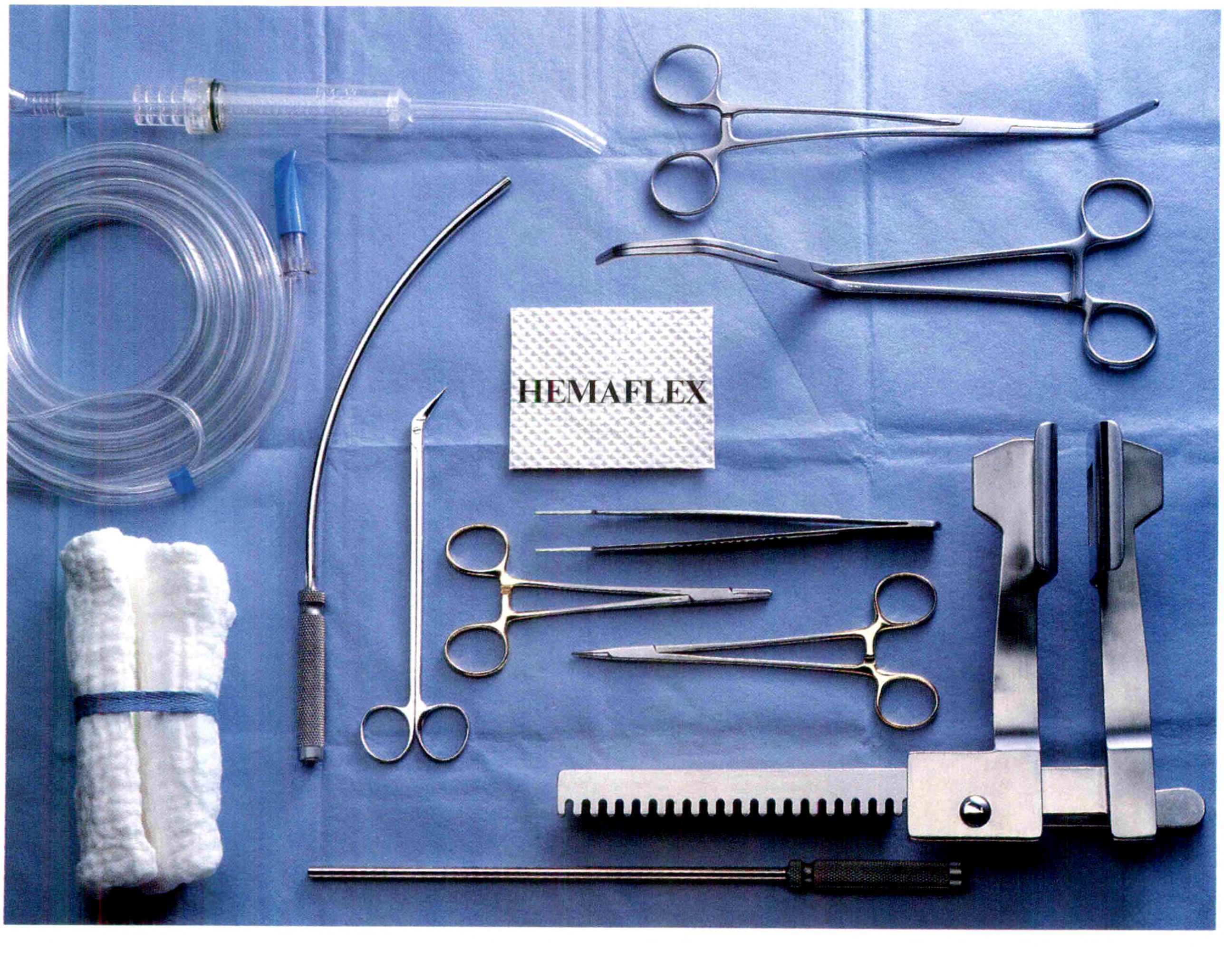

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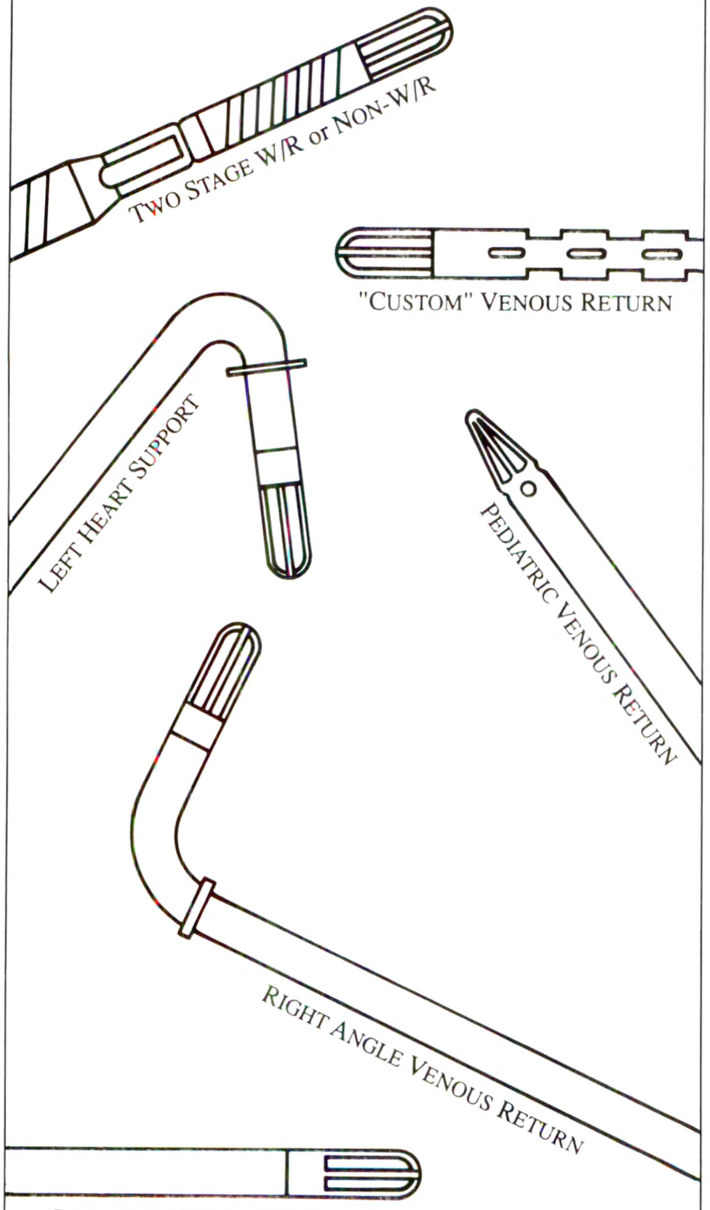

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Indications

Pericardial valves are indicated for use in patients suffering from valvular heart disease. Aortic valvular heart disease is a condition involving any of the following: obstruction of the aortic heart valve or stenosis; leakage of the aortic valve, known as regurgitation, incompetence, or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions.

Aortic valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, and rheumatic heart disease.

Pericardial valves are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards® pericardial valve is intended for use in patients whose aortic valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic valve prosthesis that is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium-metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on a maintenance hemodialysis. Clinical data which establishes the safety and efficacy of the valve for use in patients under the age of 20 is not available; therefore, we recommend careful consideration of its use in younger patients.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment. Overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to the replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis.

Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except where contraindicated) during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall, or history of previous atrial thrombus. However, the appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards® pericardial valves must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards® pericardial valve could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in the sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C and 25°C (50-77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with the eyes, seek medical attention. For more information about glutaraldehyde exposure refer to MSDS BAX 10424, available from Edwards CVS Division.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days), necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards® bioprostheses compiled from the literature and from reports received through the complaint handling system in accordance with the United States (Federal) regulations establishing Good Manufacturing Practices, Section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, and malfunctions of the valve due to distortion at implant, fracture of the Elgiloy wireform, or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and leaflet detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards® pericardial bioprostheses to calcification as compared to commercially available bioprostheses.

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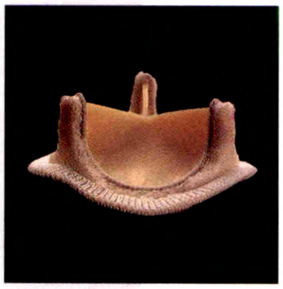

On the inside, a superior understanding of bioprosthesis design is even more evident.

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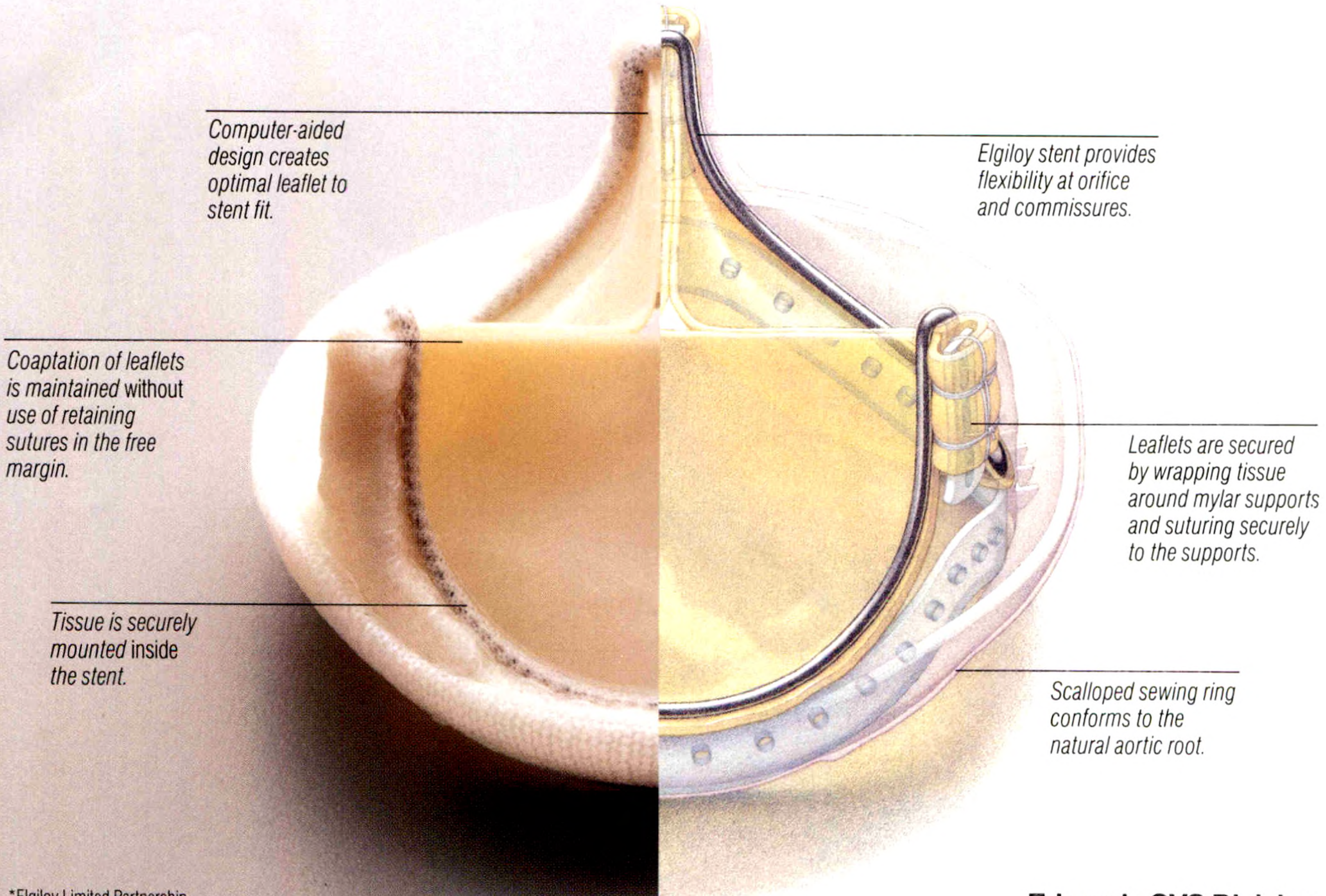
Computer-aided design creates optimal leaflet to stent fit.
Elgiloy stent provides flexibility at orifice and commissures.
Coaptation of leaflets is maintained without use of retaining sutures in the free margin.
Leaflets are secured by wrapping tissue around mylar supports and suturing securely to the supports.
Tissue is securely mounted inside the stent.
Scalloped sewing ring conforms to the natural aortic root.

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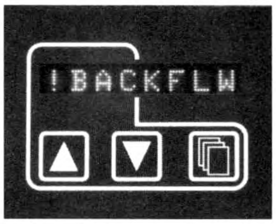
Pressure and flow dynamics of centrifugal pumps

Because centrifugal pumps are non-occlusive, flow may be antegrade or retrograde. Backflow can occur so quickly that there isn't even time to clamp the arterial line.[1]

Centrifugal pumps operate by creating pressure. Thus, flow rates are dependent on patient pressure and resistance in the circuit. For forward flow to occur, pressure in the pumphead (P_P) must be greater than the combined patient pressure (P_{PT}) and the pressure head (P_H). Retrograde flow can create a "hemodynamic siphon"[1] which may, if left unchecked, result in exsanguination or air embolization.

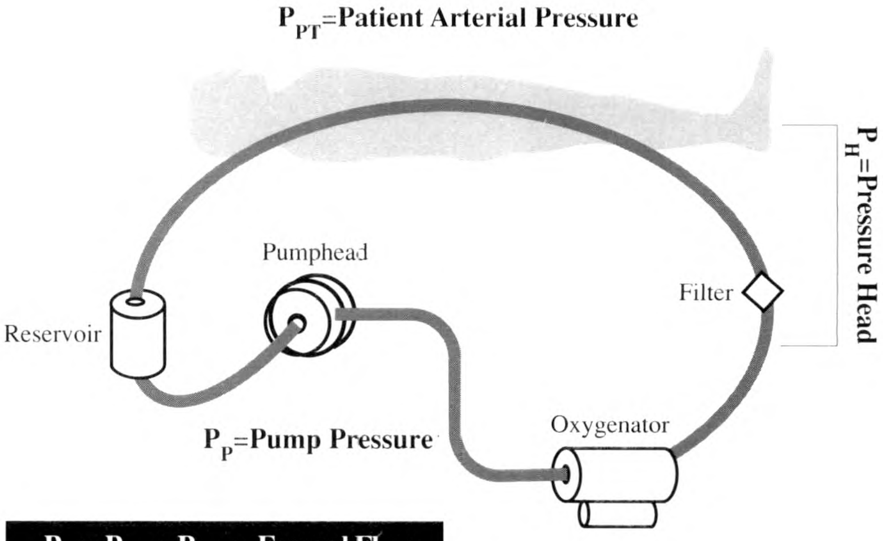
Exclusive backflow warning system

The new Sarns™ Delphin ™ II centrifugal pump system features an exclusive backflow warning system (patent pending). The directional flow sensor works with the two-level warning system to allow timely and appropriate preventive action.

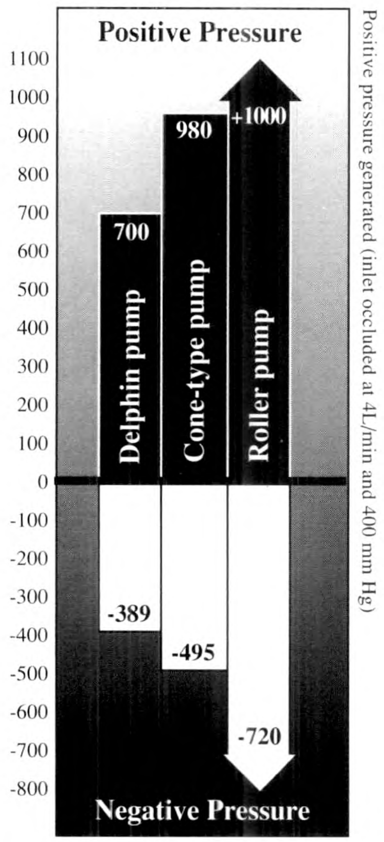


The Delphin II backflow warning system allows timely and appropriate preventive action in the case of retrograde flow.

The first "check flow" alert registers a pending backflow condition. When backflow is actually detected, a second level audible alarm notifies the perfusionist, allowing for immediate intervention. Alerts can be customized to sound once or repeat at 10-second intervals. Repetitive alerts are particularly helpful in critical care or transport settings outside the OR. Alarms, because of their critical nature, repeat at 10-second intervals.



$P_P > P_{PT} + P_H$ => Foward Flow



The Delphin pump provides protection against blowouts and against cavitation by generating the lowest levels of positive or negative pressure.

Pressure limitation

As a class, centrifugal pumps generate lower maximum pressure than roller pumps. The mechanics of centrifugal pumps effectively limit circuit pressure to provide protection against blowouts (the result of excessive positive pressure) and against cavitation (which can be caused by excessive negative pressure).

Limited positive pressure

In a roller pump circuit, accidentally kinking or occluding the arterial tubing can generate sufficient pressure within the system to blow a line or cause blood vessel injury. Non-occlusive centrifugal pumps effectively limit circuit pressure to guard against such contingencies.

Less risk of cavitation

Cavitation, the sudden formation of micro-bubbles in solution, is caused by negative pressure. Although all centrifugal pump manufacturers warn against clamping the inlet line to the pump, it may accidently be occluded. A more common danger for cavitation occurs in applications where a venous reservoir is not used, such as femoral-femoral bypass. In such situations, volume return is limited and the centrifugal pump is being used for active suction. Should the pump inlet be occluded, the Delphin system produces less negative pressure than other pumping systems (for equivalent flow rates and pressure readings).

Pressure advantages

The pressure advantages of the Delphin pump can be traced, in large part, to the efficiency of its fins. Their design not only limits positive outlet pressure, but also curbs potentially destructive negative inlet pressure. The Delphin pump demonstrates its superior efficiency by requiring fewer RPMs than other centrifugal pumps to obtain equivalent flow rates.

For more information about the Delphin II centrifugal system, call **800/521-2818**.
Or write Sarns, 3M Health Care, 6200 Jackson Road, Ann Arbor, MI 48103.

Footnote

1. Kolff J, McClurken JB, Alpern JB. Beware centrifugal pumps: Not a one-way street, but a potentially dangerous "siphon." *Ann Thorac Surg*. 1990;50(3):508.

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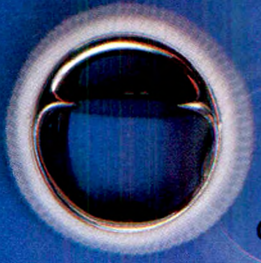

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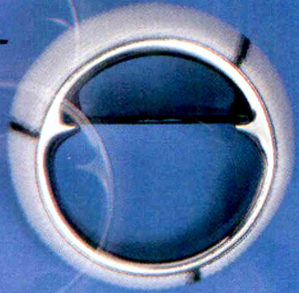

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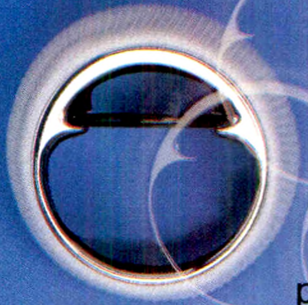

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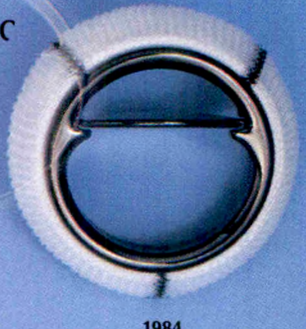

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Carpentier-Edwards® Duraflex™ Models 6625LP and 6625-ESR*-LP
Mitral Low Pressure Bioprostheses
For Single Use Only

Design

As compared to other types of prostheses, preserved porcine bioprostheses exhibit certain potential advantages: the need for long-term anticoagulation may be minimized; and although the durability of porcine bioprostheses is a limiting factor in long-term evaluation, tissue degradation is usually progressive and symptomatic, thereby permitting detection with proper annual follow-up in person with a physician, and elective intervention when necessary.

Models 6625LP and 6625-ESR-LP Mitral Carpentier-Edwards® Duraflex™ Bioprostheses are comprised of porcine aortic valves that have been preserved in buffered glutaraldehyde and then mounted on flexible frames. Glutaraldehyde is shown to both reduce the antigenicity of porcine xenograft valves and increase tissue stability.

The frame is designed to be flexible at the orifice as well as at the commissures. The compliance of the stent's commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The flexibility of the orifice is intended to reduce the loading shock at the base of the leaflet. The flexible orifice concept is based on the physiology and mechanics of natural heart valves and reported experience with implantation of unstented homografts.

The lightweight frame is made of Elgiloy,** a corrosion-resistant alloy, chosen because of its superior spring efficiency and fatigue-resistant characteristics.

The metal frame is covered with a porous, knitted polytetrafluoroethylene cloth to facilitate tissue ingrowth and encapsulation. The inflow orifice is contoured to support the right coronary cusp of the porcine valve. The commissure supports are not equidistant to conform to the anatomical configuration of the porcine aortic valve. The suture ring has a soft, silicone-rubber insert that is covered with a porous, seamless polytetrafluoroethylene cloth. The compliant nature of the suture ring facilitates coaptation between the valve and an often irregular or calcific tissue bed.

The porcine aortic valves are fixed in buffered glutaraldehyde, and then mounted on cloth-covered frames. After mounting, the valves are tested *in vitro* to ascertain their competency and flow characteristics. After final inspection, the valves are sterilized, rinsed, and then transferred into fresh glutaraldehyde and packaged under aseptic conditions.

Low Pressure Fixation

In vitro studies by Broom, et al., advise that to maintain optimum mechanical properties in the fixed porcine aortic leaflet tissue, the full collagen waveform or crimp originally present in the relaxed fresh tissue should be retained. In addition, these studies show that the collagen waveform is sensitive to alteration at fixation pressures as low as 4 mm Hg. Edwards CVS Division has developed a process to fix porcine aortic valves at a hydrostatic pressure less than 4 mm Hg to minimize alterations in the collagen waveform of the aortic valve tissue. Low pressure fixation of Carpentier-Edwards Duraflex™ bioprostheses is intended to increase the clinical durability of these valves; however, data regarding Carpentier-Edwards Duraflex™ bioprostheses are insufficient to demonstrate that durability has been increased by this preparation technique or that calcification has been reduced.

Indications

Bioprostheses are indicated for use in patients suffering from valvular heart disease. Mitral valvular heart disease is a condition involving any of the following: obstruction of the heart valve or stenosis; leakage of the valve, known as regurgitation or insufficiency; and combination of the two, sometimes referred to as mixed disease or combined lesions.

Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease, and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia.

Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpentier-Edwards Duraflex™ bioprosthesis is intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on maintenance hemodialysis.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after carefully evaluating the short- and long-term risks and benefits to the patient, and considering alternative methods of treatment. The overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of tissue valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (See Clinical Experience).

Careful and continuous medical follow-up (at least annually by a visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. Please refer to the most recent Clinical Experience attachment for data on anticoagulation relating to these valves. The appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpentier-Edwards Duraflex™ bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across Carpentier-Edwards® Duraflex™ bioprostheses could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in a sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 10°C (50°F) and 25°C (77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact with the eyes, seek medical attention.

Surgical Precautions

The models 6625LP and 6625-ESR-LP Duraflex™ mitral valves are unapproved for indications other than mitral valve replacement.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpentier-Edwards Duraflex™ bioprostheses, compiled from the literature and from reports received through the complaint handling system in accordance with the United States (federal) regulations establishing Good Manufacturing Practices section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period, and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards Duraflex™ bioprostheses to calcification as compared to other commercially available porcine valves.

See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

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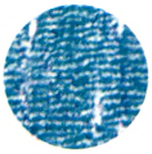

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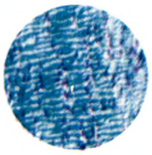

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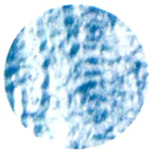

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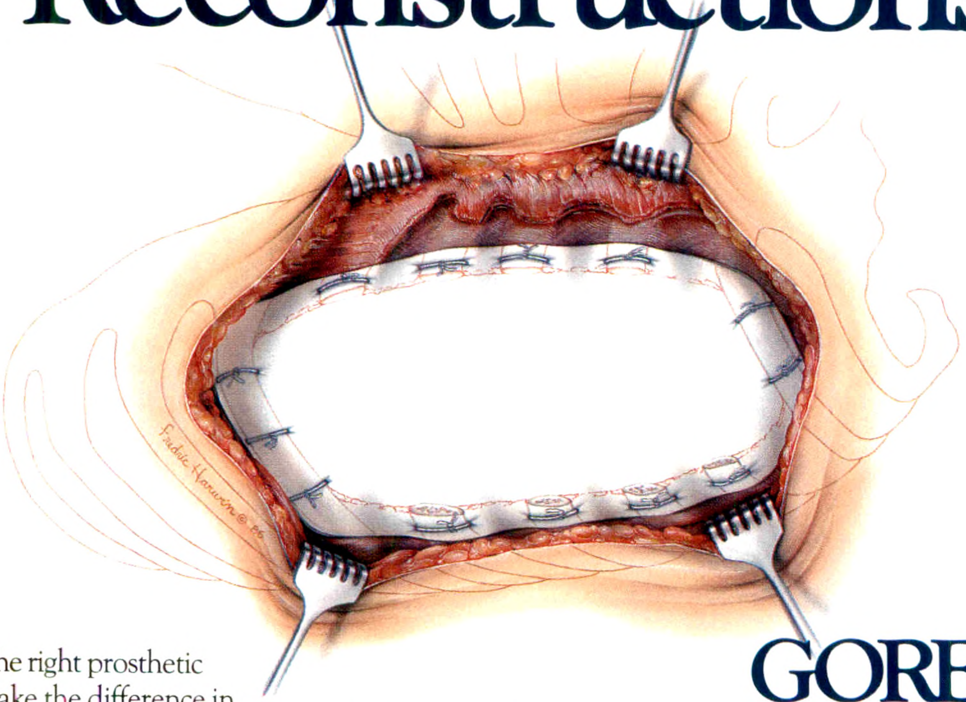

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Surgical Repair of Aortic Arch Interruption

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A single reparative operation would be preferable to a staged approach in which two or more operations eventually achieve complete repair. For most congenital heart lesions, complete repair is now the accepted standard. There are a few complex lesions, however, for which controversy continues between primary and staged approaches. Among these are the treatment of the hypoplastic left heart syndrome, in which transplantation becomes the one-stage reparative operation, as well as the severe end of the pulmonary atresia/intact ventricular septum spectrum. Repair of the interrupted aortic arch (IAA) complex, which, at minimum, includes a ventricular septal defect and a patent ductus arteriosus, also currently engenders debate. The report in this issue by Griffin and associates [1] will add to this controversy by providing another approach, which lies between the complete primary repair and the staged approach and which uses a conduit to restore arch continuity.

Each method has technical and management advantages and disadvantages, which prompts a review of these and an examination of the current available results.

See also page 430.

Although the available approaches continue to change, it is apparent that several important questions remain unanswered. The uncertainty relates to technical considerations, the effectiveness of newer approaches such as balloon dilation of anastomotic narrowings, and the lack of adequate long-term data. Only with time will these issues be settled and a clearer idea gained of which approach will yield the best chance for a favorable outcome for any given infant.

There are technical points regarding the operations themselves, and new questions will be raised by the report of Griffin and associates [1]. Under circulatory arrest, complete primary repair probably is, paradoxically, the easiest operation to perform. With thorough mobilization of the proximal and distal aorta, an adequate anastomosis can be performed. What has not been well documented is the incidence of compression of the right pulmonary artery or the left main bronchus after primary repair. Although these problems may not be common, personal communications have established their occurrence.

Placement of an 8-mm or 10-mm polytetrafluoroethylene graft using partially occluding aortic clamps as described is relatively exacting [2]. It seems likely that a primary repair using a similar technique will be equally demanding. With type B interruptions, the ascending aorta may only be 5 to 6 mm in diameter, and preservation of carotid flow can only be achieved with careful clamp placement after freeing the adventitia circumferentially. In all our cases, (18/20 type B) the grafts were placed to the ascending aorta. In at least 1 of the 4 cases of Griffin and associates [1], however, the anastomosis was placed to the left carotid artery with subsequent residual gradient. Clearly, the main technical question will be whether or not a satisfactory primary anastomosis can reliably be carried out with a low incidence of residual gradients using partially occluding clamps. This would seem to be a challenging goal. The early results are promising but lacking in detail.

It is important to define the patient population. The group of type B (or type C) infants would be considered the most difficult to repair by whatever approach. A type A IAA with interruption between the left subclavian artery and the descending aorta resembles more a severe coarctation of the aorta than a type B IAA and would be most amenable to direct repair by the lateral approach. There was a high percentage of type A infants in the series of Griffin and associates [1], and the brief summary of results unfortunately was not broken down as to type B or type A. Certainly, the ascending aorta in type B patients tends to be very small; a 6-mm ascending aorta represents the norm in our experience. If the direct repair in type B IAA by the method of Griffin and associates [1] is frequently made to the left carotid artery, then it will likely be much less satisfactory.

Moreover, the presence of serious associated lesions would be expected to increase the risk of complete primary repair. In our series, the occurrence of an anomalous origin of the right pulmonary artery from the aorta seemed to pose particular difficulty for a complete primary repair. The absence of a right pulmonary artery arising from the main pulmonary artery meant a left shift of the main pulmonary artery. After repair, tension between a primary right to main pulmonary artery anastomosis would be increased by the tension of a primary ascending to descending aortic anastomosis. Primary repair of the pulmonary artery would not seem possible except in the staged approach.

Operative survival is a reasonable beginning point for the discussion of results. Even this relatively well-defined question cannot be easily answered. As with repair of other lesions, the results continue to improve. Survival rates after complete primary repair for the last 5 or so years are now 82% [3]. We [2] have found a similar improvement with staged repair and over a similar span have achieved 100% survival despite the presence of other serious cardiac lesions. The results with the direct repair

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by the lateral approach have been less good; however, it is a small series and the differences may not be significant [1]. Whatever the approach, survival rates now are very good. Much of the improvement may be because preoperative resuscitation of these often critically ill newborns is now much better and they go to the operating room generally in satisfactory condition. Nevertheless, we believe that a small but real percentage of these infants will be ill-suited to the stresses of complete repair, and this may account for the continuing survival rate differences between complete and staged repair.

There are several obvious potential complications associated with either primary or staged repair. By and large, however, the incidence of these have not been well documented and are not useful in deciding among approaches. As recently stated, the neurological problems associated with the repair of congenital heart defects should now be a major topic of consideration [4]. All three approaches contain the potential for serious neurological injury. The need for circulatory arrest during complete primary repair raises the question of the incidence of serious neurological problems including choreoathetosis after operation [5]. On the other hand, the placement of a partially occluding clamp on the ascending aorta in the staged approach also produces the opportunity for neurological injury. We have been able to place the conduit on the ascending aorta and monitor the pressures either in the right arm or carotid artery in all our patients. To date, no instance of neurological injury attributable to the first-stage aortic arch reconstruction has occurred. The authors of the lateral approach state there were no long-term neurological problems whether or not the left carotid artery was included; however, seizures were encountered in 2 infants. This important question will require more detailed follow-up analysis.

Other important questions remain unanswered. The staged repair necessarily means two operations will be required to complete the initial complete repair. Because a nongrowing aortic graft only 8 or 10 mm in diameter is commonly used in the staged repair, a third operation to enlarge the transverse aortic arch will be necessary. Therefore, the staged approach using a nongrowing conduit segment to span the interruption will require three operations, which remains the principal drawback to this approach.

The advocates of both the primary and now the lateral direct approach cite fewer operations as an important reason for their approach. Closer inspection, however, reveals that this may not necessarily be true. The longitudinal study of the Boston group has shown that obstruction at the anastomotic site will develop in essentially all of these infants [3]. An anastomotic narrowing is a relatively difficult problem to approach primarily and for their small operative experience carried a 50% mortality [3]. Balloon dilation is now their approach, but there is no long-term information on the results. If balloon angioplasty with or without the placement of stents proves satisfactory to relieve these anastomotic obstructions, it will be an important point in favor of the direct primary repair. Presumably, this technique would also be applicable to relieving aortic anastomotic obstructions after the direct repair by the lateral approach. If, on the other hand, angioplasty techniques do not prove satisfactory to keep up with the expected considerable growth of these children, placement of a conduit to relieve the obstruction would be the simplest and safest approach. This solution would reduce the operative difference between an initial staged approach or primary repair approaches.

A staged approach with direct primary repair as described by Griffin and associates [1] could prove to be the most satisfactory. The drawbacks of complete primary repair could be reduced, whereas nonoperative solutions to the late development of anastomotic obstructions could be dealt with by angioplasty techniques. Clearly, long-term information will be necessary to settle this issue.

Of considerable interest is the associated left ventricular outflow tract obstruction seen in this lesion complex. We have noted with surprise that the incidence of this potentially severe problem has been low using the staged approach [2]. This is opposite to earlier predictions in which a pulmonary artery band was thought to enhance development of left ventricular outflow tract obstruction [6]. We do not have an explanation as to why this was less frequent in our series as opposed to the Boston series [3]. This may be due to chance alone; on the other hand, there may be unknown factors at play. Again, long-term follow-up will be necessary to settle this question.

In summary, the technique of Griffin and associates [1] adds another approach to the surgical treatment of IAA. Producing a generous primary aortic anastomosis off bypass would seem to be challenging technically. Greater experience with type B IAA and more detailed follow-up will be needed to determine the success of this otherwise promising repair. Advocates of a staged approach base their preference on better survival rates and lower incidence of neurological complications—particularly when additional important lesions are present. As of now, the data are too incomplete to dispel this controversy. I anticipate that with further improvements and additional information the choice will become clearer.

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Endothelial Covering of Biological Artificial Heart Valves

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Normal heart valves are covered with a single layer of endothelium [1]. There is a large and rapidly expanding body of data on the various functions of vascular endothelium [2], but relatively little that deals specifically with valvular endothelium. However, one extrapolation from the vascular system seems eminently reasonable: it would seem very likely that an intact valvular endothelium guards against platelet/fibrin deposition on valvular surfaces. Platelet/fibrin deposition, in turn, may lead to fibrous tissue replacement with thickening and stiffening of the cusp, may be a nidus for bacterial infection, and may be the origin of nodules of extrinsic calcification [3, 4]. The absence of an endothelial covering on glutaraldehyde-preserved bioprosthetic valves at the time of implantation has been thought to allow plasma protein insudation into the substance of the cusps. Plasma insudation, in turn, has been implicated as a cause of calcification within the substance of cusps [5].

The cusps and chordae of prolapsing incompetent mitral valves have shown patchy denudation of endothelium [6]. Specimens that we have examined of chronic recurrent mitral stenosis due to progressive thickening and stiffness have shown surfaces completely devoid of endothelium (Frater RWM, unpublished data). In both cases, the absence of endothelium may be related to thromboembolism or endocarditis. In chronic rheumatic disease the complete denudation may lead to progressive generalized loss of flexibility.

See also page 487.

Finally, neither stent-mounted, glutaraldehyde-tanned xenograft bioprostheses nor free-hand aortic homografts appear to acquire a confluent covering of host endothelium. It is possible that the calcification of tanned bioprostheses and progressive thickening and stiffening of homografts may bear some relationship to this fact.

It is clear from all of this that there are many potential advantages in having a living endothelial covering on biological artificial heart valves. Advocates of cryopreservation of homografts have assumed that the cryopreservation process certainly results in the maintenance of viability of the transplanted fibrocytes and possibly also of the endothelial cells, and that this "viability" will result in better long-term valve survival [7]. In fact, the viability of endothelial cells declines very rapidly after death and is minimal at 48 hours [8]. Unless the cryopreservation process is applied very early, there are unlikely to be viable endothelial cells on homograft valves. This may be an advantage because the antigen expression of human valvular tissue is mainly localized to the endothelium [8, 9]. It has been suggested that the occurrence of early and rapid homograft failure is related to the presence of high cellular viability [10, 11]. From this we conclude that if endothelium is to be useful on biological valves it should be host endothelium.

Although many possibilities come to mind, two major ways in which the goal of a host endothelial-covered valve could be achieved would be: (1) extracorporeal culture of host endothelial cells and in vitro seeding of devices before implantation and (2) overgrowth by host endothelial cells in vivo.

Eberl and associates [12], in this issue of *The Annals*, report on the growth behavior of endothelial cells on allograft aortic valves. They are careful to describe and define in detail the conditions of storage and preservation and the subsequent preseeding preparation of the aortic leaflets, as well as both the cultivation and seeding of the endothelial cells. It is worth noticing that these valves are stored in nutrient-antibiotic solution at 4°C rather than cryopreserved. In addition, the experiment included one group exposed for 30 minutes to 0.25% glutaraldehyde and one group tanned with 0.5% glutaraldehyde in a manner similar to that used for commercially produced xenograft valves. Four clear conclusions emerge from this study: (1) Endothelium grows well on the untanned allograft. (2) A half-hour exposure to very dilute glutaraldehyde does allow successful endothelial seeding, but changes some details of the endothelial growth. (3) Glutaraldehyde tanning completely prevents endothelial seeding. (4) In vitro endothelial seeding of valves involves a quite complex series of maneuvers for the procurement of cells and their subsequent covering of the valve surface. Furthermore, these maneuvers take time that is measured in days. In other words, there will be a price to pay for producing an endothelial covering in vitro. In the case of homograft valves, whatever advantage cryopreservation provides will be lost during the seeding process unless it can be very considerably accelerated.

The alternative approach is to implant biological valves that will allow or encourage the development of a host-

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derived endothelial covering. We have implanted stentless chordally supported mitral bioprostheses in weanling sheep. The valves have been made of bovine pericardium treated with (a) 0.625% glutaraldehyde and stored in 4% formaldehyde, (b) 99.5% glycerol, or (c) 99.5% glycerol with 24-hour exposure to 4% formaldehyde for sterilization.

Only 1 of 6 valves in group A acquired a host endothelial covering during a mean 210 days of implantation, whereas all 6 in group B were covered during a mean 167 days of implantation ($p < 0.02$). Even the brief exposure to aldehydes of the group C sheep led to severe inhibition of endothelial growth, with coverage occurring in 13 of 21 animals during a mean implantation time of 185 days (B versus C, $p < 0.05$). However, when the group C animals with implantation times of more than 200 days are examined (mean implantation time of 246 days), 8 of 9 had developed an endothelial covering [13].

The deleterious effects of residual aldehydes are thus evident in vitro and in vivo. The avoidance of aldehydes in treating bioprosthetic material is one approach in the effort to obtain endothelial covering. An alternative approach is to treat tanned tissue with the intent of reducing the toxicity of the aldehyde groups. We are encouraged by our results with this approach. Moritz and co-workers [14] from the University of Vienna have demonstrated that postfixation L-glutamic acid treatment of glutaraldehyde-tanned bovine pericardial arteries results in improved spontaneous endothelialization. It is likely that the L-glutamic acid treatment neutralizes the effect of residual free aldehydes in the tanned tissue. Because residual free aldehydes have also been implicated in bioprosthetic calcification and their elimination with reduction in calcification [15], the production of biological replacement valves that either are successfully given or acquire a covering of host endothelium and do not calcify is now a realistic possibility.

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Choices, Chances, Values

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We surgeons can improve our clinical decisions. To do so, we will need to understand that we are overconfident about the quality of our intuitive judgments, and we will have to become comfortable with a vocabulary that is unfamiliar to most of us.

Surgeons are subject to the same limitations in the way the human mind works that affect everyone else. Regardless of effort, exhortation, or training, none of us can keep more than a handful of variables in conscious attention at once; none of us can resist being disproportionately influenced by our most recent, most salient, most familiar experiences; none of us can intuitively estimate probabilities accurately. We make substantively complex judgments *as if* they were simple, because we attend to only a few variables when we decide. The clues we attend to are not always the most important factors. The language in which we discuss likelihood is imprecise: "rare" means to one physician what "frequent" means to another, if our estimates are calibrated on a numerical scale [1]. We do not reliably come to an intuitive decision that is internally consistent with our own estimates of the probabilities of important outcomes. Few of us understand that an explicit decision rule, even a simple one, outperforms clinical judgment. Expert opinion, even of august consensus panels, is no substitute.

See also page 493.

These assertions may be unwelcome, but the research on which they are based is solid. The compendia edited by Kahneman, Slovic, and Tversky [2] and by Arkes and Hammond [3] are excellent guides to the primary data. What is new to surgeons is our slowly growing recognition that the implications of such research apply to real people, real problems, and real costs, whether measured as human suffering or as resource consumption.

In this issue of *The Annals*, Olak and Detsky [4] propose a decision analysis model for addressing an interesting, controversial, clinically important issue. Whether the elements of their model, or the data on which they depend for estimates of probability, or their method for assigning utilities are correct are discussions well worth having in their own right. The point of this editorial is to emphasize that because each decision is a synthesis of choices (options we choose among), chances (likelihoods of particular outcomes associated with each choice), and values (cost or quality or desirability of the possible outcomes), and because none of us can simultaneously integrate all this information, we can, as Olak and Detsky demonstrate, exploit a technique that allows us to bring our best efforts to bear on manageable segments of the problem, one at a time. A computer (or we, if we have the patience to do the arithmetic) can carry out the computationally trivial task which, despite its triviality, is beyond the capacity of unaided human intuition: reliably to identify the best option that is logically consistent with our own beliefs. Adding sensitivity analysis to the decision model lets us test how robust the choice is if we make different assumptions about chances or values.

Some have worried that use of quantitative analytical methods diminishes the "art" of medicine. I cannot reconcile (a) rejection of techniques that demonstrably improve our ability to make good decisions with (b) our commitment to reducing the impact of human illness.

The need to make decisions in the face of uncertainty is a fact of life that is especially poignant for surgeons. Our judgment and skill are brought into question by realities like obstructions, leaks, infections, prolonged lengths of stay, hospital mortalities, and hosts of other measures. We are tempted to look back from adverse outcomes with a presumption that something should have been done differently [5, 6]. Quantitative, probabilistic analysis can identify the best decision available to us, given what we believe at the time. Whatever the consequence (because no one can guarantee a particular outcome), we can defend the rationality of our choice. Breaking decision problems into components helps us to think more clearly about them, and helps identify areas for research, so that we can set out to make the chances of obtaining a good outcome different from what they are today.

Choices, chances, values. We can do better.

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Intraoperative Aortic Dissection

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Intraoperative aortic dissection is a rare but potentially fatal complication of open heart operations. If the dissection is promptly recognized and repaired, however, the outcome may be significantly better. In this study, we reviewed the hospital records of patients with dissection of the aortic arch occurring as a complication of a cardiac operation at Massachusetts General Hospital and Mt. Auburn Hospital from January 1980 through June 1990. During this period, 14,877 surgical procedures with the use of cardiopulmonary bypass and aortic cannulation were performed, and 24 patients (0.16%) with iatrogenic aortic dissection were identified. Dissection was discovered intraoperatively in 20 patients and postoperatively after complications developed in 4. Of the 20 patients whose injuries were discovered intraoperatively and repaired, 4 (20%) died. Of the 4 whose injuries were discovered after operation, 2 (50%) died. The primary cause of death was ventricular dysfunction resulting from myocardial ischemia. Dissections originated at the aortic cannulation site in 10 patients, at the cross-clamp site in 8, at the site of the partial-occlusion clamp in 7, at the proximal anastomosis in 1 patient, and as a result of direct injury in 1. Three of these patients had simultaneous injuries at the aortic cannulation site and at the heel of the partial-occlusion clamp. Two techniques of repair were used: primary repair and patch or tube graft insertion. There were two deaths in the patients who underwent primary repair and four deaths in patients requiring graft replacement. Although it is uncommon, intraoperative aortic dissection can be a lethal complication of cardiac operations. Prompt recognition and repair are necessary to limit the extent of dissection and minimize patient morbidity and mortality.

(Ann Thorac Surg 1992;53:374–80)

Intraoperative aortic dissection is a rare but potentially fatal complication of cardiac surgical procedures. Dissections can originate at any site of intimal disruption and can present as enlarging hematomas, bleeding at sites of perforation, or bleeding from proximal coronary artery anastomoses or aortic suture lines. Intimal injury can be the result of direct laceration, mechanical compression, or torsion of the aorta. Patients predisposed to aortic injury are those with the following conditions: severe atherosclerotic changes in the aortic wall, a thin or dilated ascending aorta, cystic medial necrosis, or collagen vascular disease [1–4]. By recognizing the population at risk and then using a gentle operative technique in such patients, the surgeon can usually avoid iatrogenic injury to the aorta. In patients in whom dissection does complicate cardiopulmonary bypass procedures, however, prompt recognition of the dissection process and expeditious surgical repair are necessary to achieve a successful outcome.

For this report, we reviewed the experience of Massachusetts General Hospital and Mt. Auburn Hospital with intraoperative aortic dissections from January 1980 through June 1990. During this period, aortic dissection developed in 24 patients as a complication of cardiopulmonary bypass operations with aortic cannulation. (Two patients with retrograde dissection from femoral cannulation were excluded from this study.) Management of these patients was directed by the location and extent of dissection, and the outcome was dependent on the prompt recognition and repair of the injuries.

Material and Methods

Of the 14,877 patients undergoing procedures with the use of cardiopulmonary bypass and aortic cannulation at Massachusetts General and Mt. Auburn Hospitals from January 1980 through June 1990, 24 were identified as having aortic dissection, an incidence of 0.16%. The hospital records of these patients with acute aortic dissections were reviewed. There were 14 men and 10 women, ranging from 52 to 86 years of age (mean age, 67 years). Operative procedures included coronary artery bypass grafting alone in 17, mitral valve replacement and coronary artery bypass grafting in 2, aortic valve replacement and coronary artery bypass grafting in 1, left ventricular aneurysmectomy and coronary artery bypass grafting in 1, left ventricular aneurysmectomy in 1, aortic valve replacement in 1, and composite aortic valve and aortic root replacement in 1 (Table 1). Twenty patients had angina, and 16 patients had impaired left ventricular function confirmed by cineangiography. Twelve patients had preexisting hypertension, 4 had experienced a previous myocardial infarction, and 1 patient had undergone preoperative intraaortic balloon pump placement for uncontrolled angina. One patient had a left ventricular aneurysm, and 1 had an aneurysm of the ascending aorta.

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Table 1. Summary of Operative Data on 24 Patients With Aortic Dissection

Variable	No. of Patients
Initial Procedure	
Isolated CABG	17
MVR + CABG	2
AVR + CABG	1
LVR + CABG	1
LVA	1
AVR	1
Composite AVR + aortic root repair	1
Site of Injury[a]	
Aortic cannulation	10
Cross-clamp	8
Partial-occlusion clamp	7
Proximal anastomosis	1
Direct aortic injury	1
Type of Repair	
Primary repair	13
Dacron graft	7
Dacron patch	4

[a] Three patients had simultaneous injuries at the sites of cannulation and partial occlusion.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LVA = left ventricular aneurysm repair; MVR = mitral valve replacement.

Two patients had coexisting symptomatic peripheral vascular disease.

The quality of the aorta was mentioned in the operative notes of 12 patients. It was described as dilated in 7, as heavily calcified in 4, and as thin and friable in 1. The results of pathological examination of the aorta were described for 6 patients. Atherosclerotic changes were noted in 3, acute dissection with mural thrombus in 2, and calcified plaque in 1. Cystic medial necrosis was not found in any of the specimens.

In 20 patients, the dissection was recognized intraoperatively. This group comprised 12 men and 8 women ranging in age from 52 to 79 years (mean age, 66 years). Dissections characteristically appeared as a tense, circumferential dilatation and bluish discoloration of the exposed aorta. Subintimal extravasation of blood produces a false lumen that rapidly bleeds at proximal venous anastomoses, at suture lines for aortotomy closures, at cannulation or cardioplegia sites, or when incised. This profuse bleeding and the wide extent of the hematoma help to differentiate dissections from subadventitial hematomas, which are commonly seen in cardiopulmonary bypass procedures, are usually less extensive, do not have high-pressure bleeding, and are soft on palpation.

Six different cardiovascular surgeons were involved in the operations complicated by dissection. The general operative techniques for the bypass procedure were the same for all surgeons and involved initial cannulation of the aorta and venae cavae followed by construction of proximal vein anastomoses with the use of partial-occlusion clamps before the initiation of cardiopulmonary bypass. The patients were then placed on bypass, cardioplegia was delivered through the aortic root, and the distal anastomoses were performed. Hypothermia to 25° to 28°C was used. Once the anastomoses were completed, the aortic cross-clamp was removed, and the patient was weaned from cardiopulmonary bypass.

Dissections identified intraoperatively were noticed most frequently after removal of the aortic cross-clamp or the partial-occlusion clamp. In 1 patient, aortic injury occurred when the chest was opened for repeat coronary bypass grafting. In another, the pursestring sutures for aortic cannulation pulled out, and a partial-occlusion clamp that was applied to control bleeding resulted in a localized intimal tear. In 1 patient, dissection occurred during placement of the aortic cannula. The Crafoord aortic clamp, which was used to cross-clamp the aorta in the majority of patients before 1985, was involved in seven of the eight dissections associated with cross-clamp injury. A Fogarty cross-clamp was involved in the other cross-clamp injury. Injuries produced by the partial-occlusion clamps were most commonly seen at the heel of this instrument.

The most common site of aortic injury was the aortic cannulation site (10/24 patients). Injuries resulting from aortic cross-clamps occurred in 8 patients, injuries from partial-occlusion clamps occurred in 7 patients, and simultaneous injuries at the cannulation site and along the jaws of the partial-occlusion clamp occurred in 3 patients. In 1 patient, direct laceration of the aorta occurred on the opening of the chest, and in 1, dissection originated at the proximal anastomosis of a free right internal mammary artery graft.

In 4 patients, dissection was not recognized intraoperatively but became apparent after complications developed in the postoperative period. There were 2 men and 2 women in this group, ranging in age from 64 to 86 years (mean age, 71 years). Two of the patients experienced massive bleeding in the early postoperative period. One had undergone aortic valve replacement with coronary artery bypass grafting and had severe hypertension after completion of the valve replacement. Several extra pledgeted sutures were placed at the aortic cannulation site for hemostasis. Cardiac tamponade developed in the surgical intensive care unit, necessitating open chest resuscitation. The patient was returned to the operating room where an intimal tear originating at the cannulation site and extending onto the transverse aortic arch was discovered with massive bleeding from the cannulation site. The other patient was taken back to the operating room because of massive bleeding after coronary artery bypass grafting. In this patient, dissection and bleeding originating at the cannulation site were found.

Two patients had loss of pulses in the surgical intensive care unit. Both had undergone coronary artery bypass grafting. One of them had persistent metabolic acidosis and loss of the right femoral pulse. He underwent emergent arteriography, which showed a dissection originating at the aortic cannulation site. When he was returned to the operating room, the patient was found to have a disruption at the cannulation site as well as a large posterior intimal tear directly opposite the cannulation site. The other patient was noted to have a new left carotid bruit, loss of the right pedal pulses, and loss of sensation in the right foot. Arteriography revealed the dissection originating at the cross-clamp site and involving the cerebral, renal, inferior mesenteric, and iliac vessels.

Results

Intraoperative Diagnosis of Dissection

Surgical repair was performed in all patients when the dissection was diagnosed. A summary of the operative data is shown in Table 1. In 19 of the 20 patients in whom dissection was diagnosed intraoperatively, femoral cannulation was performed and the patient cooled to 18° to 20°C. During a short period of circulatory arrest, the aortic cannula was removed and the cross-clamp placed more distally on the aorta to expose the area of injury. In 1 patient with a partial-occlusion clamp injury, it was possible to repair the vessel without repositioning the aortic cannula.

Nine of these 20 patients underwent interposition grafting or Dacron patch graft repair of the injured aorta, and 11 had primary repair with pledgeted Prolene or Tevdek sutures. In all patients, the aorta was opened to assess the location and extent of intimal injury. A Dacron patch graft was used for repair in 4 patients. All had undergone coronary artery bypass grafting and had localized intimal tears: 1 at the aortic cross-clamp site, 2 at a partial-occlusion clamp site, and 1 from direct aortic laceration. In 1 patient, the dissection involved the three proximal vein anastomoses. After repair with the Dacron patch, the right coronary artery vein graft was anastomosed proximally to the patch. The left anterior descending vein graft was then anastomosed to the right coronary artery vein, and the obtuse marginal graft was anastomosed to the left anterior descending vein. Dissections in the other 3 patients did not involve proximal anastomoses. In them, the area of injury was excised and the Dacron patch sutured into position.

Five Dacron tube grafts were placed: 3 of the patients had undergone coronary artery bypass grafting, 1 had undergone left ventricular aneurysmectomy, and 1 had composite aortic valve replacement and aortic root repair. In the patients undergoing coronary artery bypass procedures, the proximal vein anastomoses were repositioned on the interposition graft or anastomosed to other vein grafts, depending on the available length of vein. The patient with the left ventricular aneurysm had extensive intimal injury originating at the cannulation site. The involved portion of the aorta was excised and the graft interposed. In the patient with composite aortic root replacement, a tear involving three quarters of the circumference of the aorta occurred because of a cross-clamp injury. This portion of the aorta was excised, and the graft was anastomosed to the distal aortic segment and then the proximal portion to the composite graft. The inner and outer walls of the distal aorta were buttressed with strips of Teflon felt.

The 11 patients who underwent primary repair had localized intimal tears that were amenable to suture repair. In 2, the dissection involved proximal vein anastomoses, which necessitated the repositioning of one proximal anastomosis and the use of this vein for the other proximal anastomosis. Two patients had continued bleeding after extensive local repair. In both, the proximal part of the aorta was wrapped with wide strips of Teflon felt. These were fashioned to avoid the proximal vein anastomoses and to fit snugly around the ascending aorta and act as hemostatic neoadventitia. This promptly arrested the hemorrhage, provided support for the injured aorta, and prevented postoperative bleeding. In the other 7 patients, intimal reapproximation and control of bleeding were achieved with local repair alone.

Of the 20 patients in whom dissection was recognized intraoperatively, 4 died. Two had undergone interposition grafting, 1 had had Dacron patch grafting, and 1, primary repair. One of these 4 patients had marked ST segment elevations inferiorly at the time of dissection and had severe right ventricular dysfunction after graft interposition. She could not be weaned from bypass and died in the operating room. Another patient, an elderly woman with severe left ventricular dysfunction, underwent quintuple coronary artery bypass grafting, and an extensive tear originating at the cannulation site developed. An interposition graft was placed, and the veins were anastomosed proximally to the graft. She died in the immediate postoperative period of severe biventricular failure. Another patient sustained a direct aortic laceration when the chest was opened for redo coronary artery bypass grafting. The injured segment was patched with Dacron, and the veins were anastomosed proximally to the patch. An intraaortic balloon pump was placed intraoperatively. However, the patient could not be weaned from bypass and died in the operating room. The fourth patient underwent mitral valve replacement and coronary artery bypass grafting with a free right internal mammary artery. An attempt at mitral valve repair was made; however, the value was too calcified to allow repair. Transesophageal echocardiography was used to monitor the repair. After removal of the clamp, the dissection was noted on transesophageal echocardiography, along with bleeding from the proximal anastomosis of the right internal mammary artery. The graft was sacrificed, and repair of the aorta was performed. A small persistent false lumen was noted after repair had been accomplished. On the fourth day after operation while the patient was in the intensive care unit, sudden arrest occurred after rupture of the false lumen.

Postoperative Recognition of Dissection

Of the 4 patients whose dissections were discovered postoperatively, 2 had repair with the use of interposition grafts and 2 had primary repair. The grafts were placed in the 2 patients loss of pulses; in both, dissection was confirmed by arteriography. One patient with persistent metabolic acidosis and loss of the right femoral pulse was returned to the operating room on the day of operation. Inner and outer layers of Teflon felt were used to support the proximal and distal aortic suture lines. Biventricular failure developed, and the patient died in the operating room. The other patient was returned to the operating room on postoperative day 2, and an interposition graft with Teflon buttressing of the proximal and distal suture lines was placed. He survived this procedure and was eventually discharged from the hospital.

The 2 patients who underwent primary repair were returned to the operating room because of massive postoperative bleeding. In both, bleeding was detected at the aortic cannulation site and repair was accomplished with pledgeted sutures. Both patients required tracheostomy for postoperative respiratory failure. The tracheostomy tube was eventually removed in 1 patient who was transferred to a rehabilitation hospital. The other patient underwent 4 months of hospitalization and then died of multiple-organ failure.

The mortality rate for the 4 patients with postoperative diagnosis of dissection was 50%. The patient who was discharged required placement of a permanent pacemaker for complete atrioventricular block caused by a perioperative myocardial infarction in the inferior wall. The other surviving patient was transferred to a rehabilitation hospital and lost to follow-up.

Comment

Intraoperative recognition of aortic dissection requires a high index of suspicion and good clinical judgment. A dissection must be differentiated from a subadventitial hematoma, which is commonly encountered during operations with the use of cardiopulmonary bypass. A subadventitial hematoma is usually small, enlarges slowly, and stops enlarging after bypass is initiated. It is soft to palpation and can be decompressed by incising the surface. A dissection, on the other hand, can rapidly involve the entire exposed aorta, giving it a tense, bluish, dilated appearance. Rapid bleeding occurs when the adventitia is incised. There can also be bleeding from proximal vein grafts or aortic suture lines. Surgeons must recognize that this complication can occur in patients in whom the aorta appears to be grossly normal [3, 5, 6], as was the case in 50% of the patients in this series.

Clearly, the prevention of aortic injury and the avoidance of dissection are preferred over treatment of this complication. Aortic cannulation, aortic cross-clamps, and partial-occlusion clamps were responsible for 25 of the 27 dissections. Techniques for avoiding these injuries have been discussed by others [4, 6–8], and several points deserve emphasis. Preventive measures that we believe to be important include control of systolic blood pressure during cannulation, placement of the aortic cannula away from aortic plaque, use of deep partial-thickness or full-thickness bites in the pursestring sutures for cannulation, use of aortic cross-clamps with padded inserts, avoidance of torsion and proximity of the heel of a partial-occlusion clamp to the aortic cannula, careful application and removal of all clamps, and reduction of pump flow during clamp application.

During cannulation, systolic blood pressure should be carefully controlled and kept lower than 100 mm Hg to prevent excessive aortic wall stress. The cannulation site should be away from palpable aortic plaque to avoid separation of the plaque from the aortic wall. Pursestring sutures for cannulation should be placed as full-thickness or deep partial-thickness bites to ensure reapproximation of the aortic intima after withdrawal of the cannula.

Preventive measures may reduce the incidence of clamp-related injuries as well. All cross-clamp injuries in this series except one occurred when a Crafoord clamp was used. We and others [1, 3] suggest the use of less traumatic hydrogrip clamps. This method appears to limit the risk of cross-clamp injuries. The injury typically encountered with the partial-occlusion clamp occurs at the heel of the clamp where the highest pressures are generated. Newer clamps with more even distribution of pressure may limit the risk of this injury. In addition, care should be taken to place the heel of the partial-occlusion clamp slightly away from the aortic cannula. Torsion on the partial-occlusion clamp closely adjacent to the aortic cannula may injure the intima. Finally, pump flow should be reduced whenever cross-clamps or partial-occlusion clamps are applied, thus reducing aortic pressure and the risk of intimal injury.

The appropriate repair for aortic dissection is determined by the extent and location of the injury. For all dissections, the torn intima must be reapproximated and the false lumen obliterated. For injuries that are proximal to the aortic cannulation site and do not involve the proximal vein anastomoses, repair can usually be accomplished by primarily reapproximating the intimal tear by use of pledgeted Prolene or Tevdek sutures. When the dissection involves proximal vein anastomoses, an interposition Dacron graft or Dacron patch graft should be constructed and the veins then reanastomosed proximally to either the Dacron graft or another vein graft (Fig 1).

If the aorta can be cross-clamped distal to the dissection without moving the aortic cannula, the repair can be performed without recannulation. For those cases in which the dissection involves or extends distal to the cannulation site, however, more distal cannulation either of the distal aortic arch or the groin with more distal aortic cross-clamping becomes necessary. Again, isolated intimal injuries can usually be approached using primary repair, whereas those involving proximal vein anastomoses require interposition grafting. As described in this series and by others [1], we favor the use of inner and outer layers of Teflon felt in both the proximal and distal suture lines of the graft interpositions to bolster the suture line repair and help obliterate the false lumen. Once the need for repair is realized, the surgeon must act quickly—to limit both the extent of dissection and the time on cardiopulmonary bypass.

The Dacron patch was used in patients with localized intimal tears that involved a broad but noncircumferential injury and in patients with heavily scarred or immobile aortas. In these broader injuries, which were usually clamp-related, repair with a patch graft could be performed without tension or distortion of the aorta. Similarly, in patients with heavily scarred or immobile aortas, most commonly seen at reoperations, primary repair without undue tension may not be possible. A patch can be placed without undue tension, and patch placement can be performed more quickly than interposition grafting.

Overall, 6 of the 24 patients with aortic dissection died,

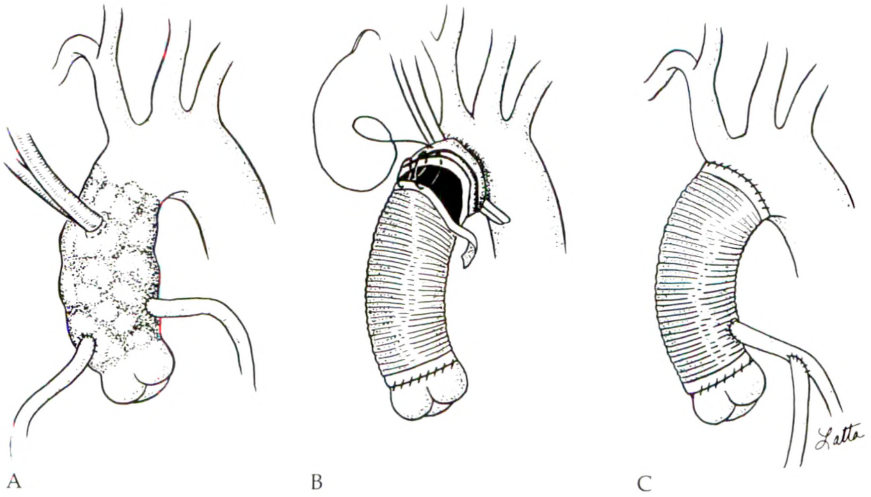

Fig 1. (A) Aortic dissection involving the cannulation site and proximal anastomoses. (B) After femoral cannulation, the ascending aorta is repaired with an interposition Dacron graft. Inner and outer layers of Teflon felt are used to obliterate the false lumen. (C) Veins are anastomosed proximally to the graft.

a mortality rate of 25%. The repair in 4 of these 6 patients involved interposition or patch grafting. All 4 died of ventricular failure in the operating room. Two patients who underwent primary repair died: 1 after a prolonged hospital course and 1 after rupture of a persistent false lumen 4 days postoperatively. (In the former case, dissection was diagnosed postoperatively because of mediastinal bleeding from the cannulation site. The patient died after 4 months of hospitalization.) It is possible that the prolongation of cardiopulmonary bypass needed to construct the graft anastomoses had an adverse effect on patient outcome. It is also possible that the more extensive injuries, which required graft reconstruction, had an adverse effect.

Murphy and associates [3] described a significant prolongation of cross-clamp time in 8 of 15 patients with dissections diagnosed intraoperatively. They attributed the 33% mortality rate in this group to subsequent myocardial dysfunction. Clearly, unnecessary prolongation of ischemic arrest is to be avoided, and careful assessment of the aortic injury is crucial. If intimal injury is amenable to primary repair, this should be the procedure of choice, thereby minimizing additional cross-clamp time. If an interposition graft appears to be needed, the repair should be expeditiously undertaken.

Although it was not used in our patients, another technique of repair as presented by Murphy and colleagues [3] deserves mention. In patients with limited dissections, they described the technique of "closed plication" in which a partial-occlusion clamp is used to encompass and limit the area of dissection. Pledgeted sutures are then placed to plicate the injured aortic site. In the Emory experience [3], this proved to be a useful technique for limiting the dissection process and quickly repairing the aorta. One limitation of this technique is that the extent of the intimal defect is never visualized; thus, in 3 of 9 patients treated by this technique, closed plication failed to arrest the dissection. In the other 6 patients, the technique was successful, and those patients did well. One further caveat would be to avoid incorporating too much of the aorta in the plicated segment. In patients with small aortas, this could result in substantial supravalvular aortic narrowing and a coarctationlike effect.

In 2 patients who underwent primary repair, bleeding from a localized segment of the aorta was noted but could be easily controlled with local finger pressure. In these patients, strips of Teflon felt were fashioned to encircle the aorta while avoiding the proximal vein anastomoses. The Teflon felt acted as neoadventitia, providing hemostasis and support to the damaged aortic segment. Although this is not a new technique, it is useful and effective and can benefit patients with friable aortas after primary or graft repair.

Postoperatively, aortic dissection can be seen as loss of pulses, ongoing unexplained metabolic acidosis, mediastinal hemorrhage, cardiac tamponade, a new murmur of aortic regurgitation, or chest pain. For patients with documented loss of a peripheral pulse, severe mediastinal hemorrhage, or tamponade, the initial diagnostic and therapeutic maneuver should be reoperation. In our series, the 2 patients with mediastinal hemorrhage were taken directly to the operating room for repair. In the 2 patients with loss of pulses in the postoperative period, arteriography was performed before reoperation. Arteriography helped to confirm the clinical suspicion of aortic dissection and disclosed the site of intimal injury. It can be argued that such information is usually evident on surgical reexploration and that application of arteriography may delay definitive repair. However, if the diagnosis is questionable or the surgeon needs to know the location of the intimal tear, arteriography is the diagnostic test of choice in the patient in hemodynamically stable condition.

The use of computed tomography and echocardiography has also been described [9, 10] and may be helpful during the postoperative period, especially in those patients who experience the onset of new murmurs or acute mediastinal enlargement on chest roentgenograms. Also, as transesophageal echocardiography becomes more routine for operations involving cardiopulmonary bypass and as greater expertise is gained in its use, this may prove to be a valuable diagnostic tool, both intraoperatively and postoperatively, for the identification of aortic dissection

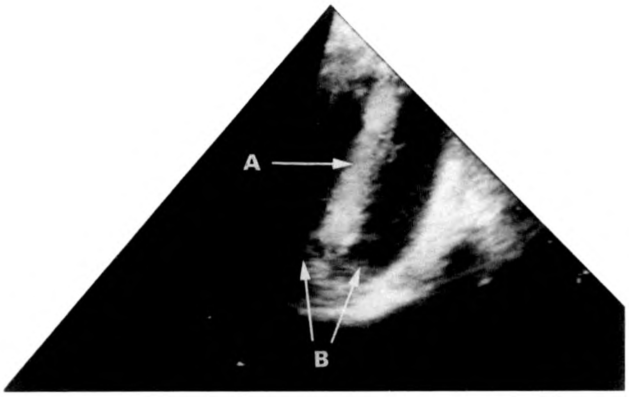

Fig 2. Transesophageal echocardiogram of aortic dissection at the level of the aortic arch. The true (A) *and false* (B) *lumens are identified.*

and evaluation of the subsequent repair [11–13]. As seen in 1 patient in our series, transesophageal echocardiography was helpful in documenting accurately the presence of a false lumen after the initial removal of the cross-clamp (Figs 2, 3). After repair, a small residual false lumen could also be seen. If, as in this patient, further attempts at repair could require reinstitution of cardiopulmonary bypass or unacceptable prolongation of the operation (in the surgeon's opinion), transesophageal echocardiography could be used to follow up the patient on a daily basis so that any enlargement in the false channel could be identified.

The medical management of any patient suspected of having a dissection requires strict control of blood pressure to limit systolic pressure and mediate the rate of pressure rise. If the clinical scenario is clear, the patient should undergo operation immediately. If not, expeditious aortography should be performed to confirm the clinical suspicion. Repair, however, must be operative, and unnecessary delays in returning the patient to the operating room for definitive repair should be avoided.

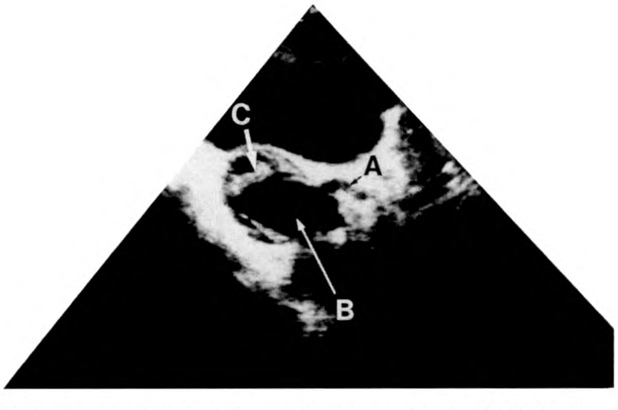

Fig 3. Cross-section of aortic root (same patient as in Fig 2) showing left main coronary artery (A), *aortic root true lumen* (B), *and false lumen with clot* (C).

Conclusion

Diagnosis of aortic dissection requires a high degree of clinical suspicion in the intraoperative and postoperative periods. Once the diagnosis is made, immediate repair should be undertaken to limit both the extent of dissection and its complications. The type of repair is determined by the extent and location of the intimal tear. Primary repair with the shortest possible bypass time is the procedure of choice in patients with localized intimal disruption. Interposition or patch grafting may be necessary for more extensive lesions; the need for this type of repair should be recognized quickly and expeditious repair performed, again to limit ischemic time. Increased mortality is associated with delay in diagnosis and with ventricular dysfunction secondary to myocardial ischemia. By recognizing those patients at risk and employing gentle operative technique, the surgical team can minimize the risk of dissection. Once dissection has occurred, however, rapid diagnosis and appropriate surgical management are necessary to improve patient outcome.

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DISCUSSION

DR JOSEPH M. CRAVER (Atlanta, GA): Dr Still has presented a very careful review of 24 patients who experienced an acute aortic dissection complicating an open heart operation. This study encompassed a 10-year span during which about 15,000 patients were operated on by the superb surgeons of Massachusetts General Hospital.

The site of the aortic intimal injury was found to be at the aortic cannulation site in 10 patients, at the cross-clamp site in 8, and at the site of application of partial-occlusion clamps in 7. In 20 patients, the dissection was discovered intraoperatively. All these patients underwent an immediate open repair using cardiopulmonary bypass and with the aortic cannula moved to the femoral artery in 19. Eleven had primary local repair with pledgeted sutures, 4 required a patch repair, and 5 had implantation of a tube graft.

When primary repair was possible, a successful outcome was achieved in 9 of the 11 patients. This high rate of success appeared to be related to three factors: a localized area of injury, an aorta of better quality, and the very short additional operative interval required to accomplish the repair. In contrast, those patients who required a patch or tube graft generally had a more extensive dissection, a more diseased aorta, and a higher incidence of preoperative left ventricular failure. Three of the nine repairs in this group were unsuccessful. All of the patients in whom the dissection occurred after they had been moved to the intensive care unit experienced difficulty, and the mortality was higher.

Many important points are made in the manuscript. The most important is that prevention is better than treatment. This starts with the recognition of aortas that are at increased risk: the dilated, atherosclerotic aortas in patients with chronic hypertension. The second point is use of less traumatic clamps on the aorta by substituting cushioned hydragrip clamps and partial side-biting clamps that distribute the pressure more evenly across the aorta. This avoids the crushing pressure so commonly noted at the heel of the clamp. The third is lowering of the systemic blood pressure or pump flow both when the clamps are applied *and* when the clamps are removed.

After a review in 1981 at Emory that showed that two thirds of all the deaths after coronary bypass procedures were related to acute aortic dissections, my colleagues and I implemented these principles. We replaced the former aortic clamp with the hydragrip clamp with cushioned inserts on both sides. We switched from a Bailey clamp to a Kay-Lambert clamp for partial occlusion of the aorta. This has reduced the incidence of dissection in our patient population, and the location and extent of the injury have also changed markedly.

We suggest that the dissection process starts usually as a localized area of injury. Unlike Dr Still and his colleagues, we believe that this can often be dealt with by an exclusion process. In 15,000 patients who underwent a cardiac operation, 27 experienced dissection. Sixteen of the 27 acute dissections were successfully controlled by partial-occlusion clamping and local buttressed repair without the need to move the cannulation site or to provide additional cardiopulmonary bypass, and with a much shorter operation.

An open repair was required in 11 of the 27 patients, and it involved either the opening of the aorta and repair with a patch or the replacement of the aorta with a tubular graft. Open repair in every case involved a higher morbidity and a longer operative procedure. It was applied when the initial dissection involved a much more extensive injury and was associated with a longer reoperative interval and an additional ischemic insult, which were not incurred by patients who were managed with the closed technique. Three of the 11 patients requiring open repair in our series died of complications of ventricular dysfunction and 1 died of late endocarditis after a successful repair.

In essence, we believe that a plication technique should be employed in every possible case to reduce the morbidity and mortality related to this complication. The area is repaired by Teflon felt–buttressed sutures to encompass the aorta well above and below the suspected site of dissection. Because the aorta is a large vessel, coarctation or any kind of pressure problem over the tangentially repaired area has not occurred. After repair and separation from bypass, careful control of the patient's blood pressure must be accomplished with pharmacological agents and maintained long term with β-blocking medication. Also, we have found that if the local exclusion repair proves unsuccessful, it does not preclude subsequent open repair.

Early recognition, local exclusion, and repair were considered responsible for reducing the mortality rate related to this severe complication from 33% in our first report in 1983 to 14% in our subsequent report published in 1989.

I have three questions. First, after your review of this experience, Dr Still, and its mortality rate of 20%, do you still believe that open repair with visualization of the intimal injury is necessary for successful repair? Second, arteriography was used in 2 of the 4 patients with acute loss of pulses in the intensive care unit. Would a more rapid diagnostic measure such as transesophageal Doppler echocardiography be sufficient now for diagnosis, or do you still think there is a need for arteriography and the delay in implementing treatment that it entails? Third, because your practice of coronary bypass grafting involves construction of proximal anastomoses for bypass grafts before the patient is on the pump and before the distal anastomoses are done, have any of your dissections occurred at this juncture? How are they managed, and was the outcome adversely affected, as the work of the original operation had to be accomplished after the injury was sustained?

DR STILL: I thank Dr Craver for his insight and comments and congratulate the Emory group on their series and their results.

To answer his first question, we do believe open repair is necessary. We think that only by opening the aorta can we be assured of complete intimal reapproximation and obliteration of the false lumen.

The second question concerned the need for arteriography postoperatively. It is probably now an acceptable alternative for patients to undergo transesophageal echocardiography to determine whether or not the dissection is present. There are currently several studies in the literature in which the sensitivity and specificity of this technique have proved that it is a valuable and accurate tool for assessing whether or not dissection is in fact present. Particularly for the patient in hemodynamically unstable condition who would not be a suitable candidate for arteriography, transesophageal echocardiography provides a safe and expeditious method of evaluating the aorta.

Regarding the use of the partial-occlusion clamp in constructing the proximal anastomoses, in 2 patients undergoing coronary artery bypass grafting, dissections were noticed before the initiation of cardiopulmonary bypass. In both patients, femoral cannulation was performed and bypass instituted. Both injuries were repaired primarily with pledgeted sutures, and the proximal anastomoses were repositioned on uninvolved aorta. One patient underwent quadruple coronary artery bypass grafting with a left internal mammary artery graft and was discharged on postoperative day 9. The other underwent triple coronary artery bypass grafting and was discharged on postoperative day 10.

Synchronous Operation for Ischemic Cardiac and Cerebrovascular Disease: Early Results and Long-Term Follow-up

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The late follow-up of 230 patients who underwent synchronous operation for extensive, obstructive extracranial and coronary artery disease from 1974 to 1989 was analyzed. Mean age at operation was 62.5 years; 161 patients (70%) were in New York Heart Association class III or IV, 185 (80%) had triple-vessel disease, and 67 (29%) had left main stem lesions of 50% or more. Previous myocardial infarctions were present in 132 patients (57%). Only 78 had normal left ventricular function. Included were 16 patients undergoing coronary reoperations, 17 patients with additional cardiac procedures, and 3 with synchronous pulmonary procedures. Symptomatic extracranial vascular disease or stabilized neurological deficits were present in 108 patients. Bilateral hemodynamically significant carotid disease was present in 91 patients and arch vessel lesions in 37. The hospital mortality in 8 patients (3.5%) was due to cardiac (n = 4), neurological (n = 1), or multiorgan failure (n = 3). Operative morbidity was mainly neurological (n = 20, 8.7%): 7 reversible deficits and 7 major strokes occurred, 2 reversible and 5 major strokes were related to the operated side(s), and 4 postoperative myocardial infarctions occurred. Actuarial survival at 5 years was 74% (±3.3), at 10 years 54% (±4.9), and at 15 years, 35% (±6.6). This was mainly determined by late cardiac death (41/66). Late morbidity was mainly attributable to cardiac causes rather than neurological causes. At 5 and 10 years, respectively, 72% and 44% of the patients were free of major cardiac and neurological events or death. Synchronous revascularization can be performed relatively safely. The long-term outcome is determined by the extent and severity of the cardiovascular disease.

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The management of patients with coexisting severe carotid and coronary artery disease continues to be controversial [1]. Some authors have advocated ignoring asymptomatic carotid stenosis [2–5]. However, the natural history studies of carotid stenosis have clarified the importance of critical carotid artery lesions [6–8]. The impact of coexisting carotid disease on the increased stroke rate after coronary artery bypass grafting (CABG) has been documented by two large prospective follow-up studies [1, 9]. The incidence of stroke in patients with asymptomatic carotid bruits, previous stroke, transient ischemic attacks (TIAs), or documented severe carotid disease undergoing CABG has been estimated in case control studies [10, 11] or comparative studies [1, 9] to be approximately 6%. Gardner and associates [10] demonstrated the additional influence of factors such as increasing age and bypass time. However, wide variations existing in the composition of published patient series with coexisting severe carotid and coronary artery disease make it difficult to reach concordant conclusions: such factors as the percentage of patients with symptomatic carotid disease or with previous strokes and the number of patients with severe bilateral disease vary from one study to another. Factors related to the indication for CABG or the accepted age limit also influence mortality and morbidity ranges. Finally, the relatively low prevalence of serious carotid artery disease in patients scheduled for CABG precludes large study populations.

Since 1974, we have advocated synchronous treatment for severe coexistent disease in specific subgroups considered to be at a higher risk for cerebral complications. We have focused mainly on the hemodynamically significant (HS) lesions of the carotid arteries, either unilateral or bilateral, and on the synchronous treatment of high-grade lesions of the arch vessels. Only a few studies have analyzed the long-term follow-up of patients with synchronous treatment of coronary and carotid lesions [1, 12]. We have analyzed the follow-up at regular intervals of up to 16 years after operation of the 230 patients operated on in our department between 1974 and January 1, 1990.

Patients and Methods

Patient Selection and Clinical Profile

The surgical candidates either were scheduled for carotid endarterectomy and found to have severe coronary artery disease or were scheduled for CABG but had neurological

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Table 1. Extent of Cardiac and Extracranial Disease in 230 Patients With Synchronous Procedures[a]

Disease	No. of Patients	Percentage of Patients
Cardiac		
NYHA III + IV	161	70
3-Vessel disease	185	80
2-Vessel disease	37	16
Left main stem ≥50%	67	29
Previous infarction(s)	132	57
Impending (recurring) infarction	58	25
Extracranial		
Symptomatic	108	47
Severe arch vessel disease	37	16
Bilat HS disease[b]	92	40
Occlusion + HS stenoses	39	17
Bilat HS stenosis	52	22
Bilat occlusion	1	. . .

[a] Sixty-eight women and 162 men; mean age, 62.5 years (range 41 to 78 years). [b] Defined as along the cerebropetal axis (innominate and/or common carotid and/or internal carotid).

Bilat = bilateral; HS = hemodynamically significant.

symptoms, asymptomatic carotid bruits, or other evidence of extracranial obstructive arterial disease: the hemodynamic significance of their extracranial lesions was assessed. Since 1976, oculopneumoplethysmography Gee (OPG Gee) has been used in the screening of patients with symptomatic lesions or asymptomatic bruits. In the presence of contralateral occlusive carotid artery disease, the hemodynamic significance was evaluated by OPG Gee criteria for bilateral lesions [13, 14]. Since 1981, intravenous digital subtraction angiography as well as duplex scanning has been used [15, 16]. Intraarterial (semi) selective angiography was only used when disagreement between investigations persisted, ie, in less than 15% of patients or in patients with unstable angina. At angiography, a stenosis was considered as HS when the diameter was reduced by 70% or more as compared with the normal distal carotid artery. In asymptomatic patients a 65% to 90% stenosis—and in the recent 5 years a 90% to 99% stenosis [17]—according to duplex criteria was necessary before a lesion would be considered for synchronous operation. We have included in the decision matrix the predicted stroke risk in the event of progression to occlusion [18, 19]; for this purpose the collateral hemispherical perfusion was evaluated. It was considered inadequate when clinical symptoms or electroencephalographic slowing occurred during carotid compression at the stenotic side or when the collateral ophthalmic artery pressure determined by compression during OPG Gee [18] was too low (40 mm Hg or less). In recent years, transcranial Doppler examination was also performed, with special attention paid to the collateral circulation in the circle of Willis. The anterior as well as the posterior collateral pathways were evaluated in order to estimate the stroke prone type of carotid lesions. A decreased vasodilatory response to CO_2 at transcranial Doppler examination was recognized as a sign of limited collateral circulation. With this selection process, only a minority of patients scheduled for CABG and having a neurological history or asymptomatic bruit(s) were considered for synchronous operation.

Due to the prevalence of severe coronary artery disease in patients scheduled for carotid artery operation, approx-

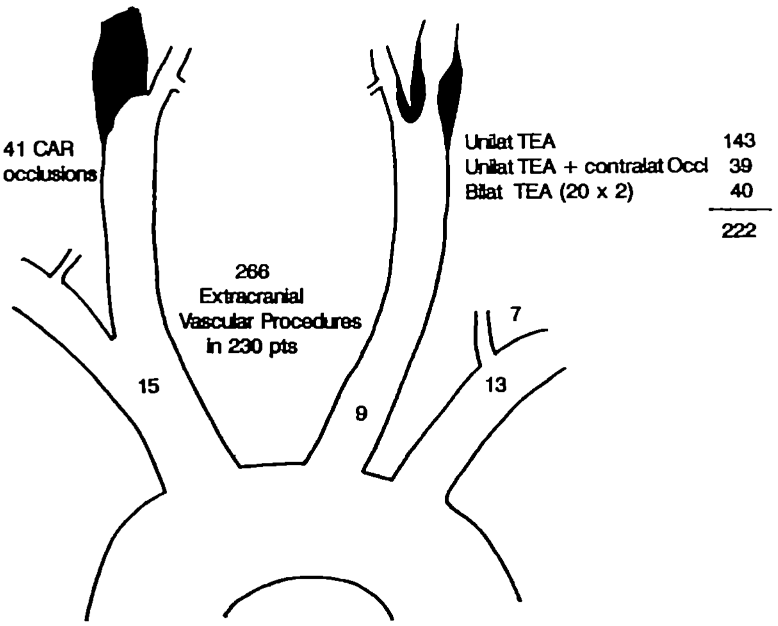
41 CAR occlusions
Unilat TEA 143
Unilat TEA + contralat Occl 39
Bilat TEA (20 x 2) 40
222
266 Extracranial Vascular Procedures in 230 pts
15
9
13
7

Fig 1. Number and localization of extracranial vascular procedures in synchronous revascularization. (Bilat = *bilateral;* CAR = *carotid;* contralat = *contralateral;* Occl = *occlusion;* TEA = *thromboendarterectomy;* Unilat = *unilateral.)*

imately 10% of candidates for carotid operation were ultimately operated on synchronously. However, only 230 patients out of 12,800 undergoing CABG operations (<2%) during this 16-year interval were operated on synchronously.

The patient characteristics regarding age, sex, and extent of cardiac and extracranial vascular disease are listed in Table 1. Preoperative cardiac status as defined by the New York Heart Association (NYHA) was based on both the degree of angina and the functional disability from congestive heart failure.

A mean number of four distal anastomoses per patient was performed, attesting to the extent of the coronary disease; 88% of all patients received three or more distal anastomoses. Direct septal artery grafting was performed in 6 patients, distal coronary endarterectomy in 15, and a left main endarterectomy in 1; since 1984, the internal thoracic artery was used in 68 patients. Left ventricular function at angiography was normal in only 78 patients (34%) and severely abnormal (more than two severely hypokinetic or akinetic segments out of five on the right anterior oblique projection) in 60 patients (26%).

The severity of extracranial disease is documented by the extent of the disease (Table 1) as well as by the presence of symptoms in 108 patients. Previous hemispheric TIAs or reversible ischemic neurologic damage (RIND) were the presenting symptoms in 12, recent hemispherical TIAs in 19, amaurosis fugax in 16, and vertebrobasilar TIAs in 15. A previous stroke occurred in 28 patients and a recent stroke of less than 6 weeks, in 3 patients.

In 37 patients, severe stenosis of the arch vessels was corrected. Bilateral HS carotid artery stenosis (n = 52) or occlusion with contralateral stenosis (n = 39) was present in 91 patients. Combinations of extracranial vascular procedures were performed, making the total number of synchronous extracranial procedures 266 (Fig 1).

Additional cardiac procedures such as left ventricular aneurysmectomy and valve reconstruction or replacement were performed where necessary. In 3 patients, synchronous lung operation was performed, and in 2 the thoracic aorta was operated on (Table 2). During the last 4 years more than 30% of the patients were 70 years old or older (Table 3).

Table 2. Type and Extent of Other Procedures in 230 Patients Undergoing Synchronous Operation

Other Procedures	No. of Patients
Reoperative CABG	16
Left ventricular aneurysm resection	4
Aortic valve replacement	7
Mitral valve replacement/plasty	4
Tricuspid valve plasty	1
Coarctation resection	1
Arch aneurysm resection	1
Bilobectomy	1
Bullectomy	2

CABG = coronary artery bypass grafting.

Operative Techniques

The carotid endarterectomy was performed first. However, it was performed after median sternotomy in unstable patients. Separate low-dose heparinization of 50 mg was used for carotid endarterectomy. Continuous electroencephalography was monitored during the carotid endarterectomy and the extracorporeal procedure. An intraluminal shunt was used when the carotid stump pressure was low (≤30 mm Hg) or when progressive diffuse or ipsilateral electroencephalographic slowing occurred during test clamping. In bilateral carotid endarterectomy, the side with the highest stump pressure was obliterated first. The neck incisions were left open until the end of the cardiac procedure. When indicated, arch vessel procedures were performed through the median sternotomy before CABG and before associated ipsilateral carotid endarterectomies. The carotid endarterectomy was performed during temporary deep hypothermic extracorporeal perfusion [20] in only 2 patients with difficult access to the carotid bifurcation and test occlusion intolerance.

Table 3. Mortality and Morbidity During Successive Years Related to Preoperative Variables

Year of operation	No. of Patients (% of n of CABG)	Preoperative (%)			Perioperative Mortality and Morbidity			Age ≥70 years	
		Infarct	3VD	LM	%	nN	nC	No.	%
1974–1977	15	60	60	33	0	0	4	0	0
1978–1981	46	54	67	24	4.4	2	2	2	4
1982–1985	87	60	88	33	3.5	5	3	12	14
1986–1989	82	56	83	27	3.7	7	0	26	32
Total	230					8	9	40	

CABG = coronary artery bypass grafting; LM = left main disease (≥50% stenosis); nC = myocardial infarction or low cardiac output; nN = severe neurological deficits (reversible ischemic neurological damage or stroke); 3VD = three-vessel disease at coronary angiography.

Table 4. Multivariate Prediction (Stepwise Logistic Regression Analysis) of Early Neurological Complications (≤30 days) in 230 Synchronous Operations

Risk Factors[a]	log Regression Coefficient	Standard Error	p Value
All events			
Presence of severe LV dysfunction[a]	0.890	0.502	0.074
Presence of preoperative neurological event			0.046
Recent TIA or AF	0.362	0.612	
Recent RIND and/or stroke + deficit	1.360	0.564	
Constant	−3.110	0.455	<0.0001
Severe events			
Constant	−3.243	0.456	<0.0001
Presence of bilateral HS disease	0.986	0.575	0.089

[a] See text.

AF = amaurosis fugax; HS = hemodynamically significant; LV = left ventricular; RIND = reversible ischemic neurologic deficit; TIA = transient ischemic attack.

Standard extracorporeal bypass perfusion techniques were used, with hemodilution to a hematocrit of 0.20 to 0.25 and perfusion temperatures of 25° to 28°C. The first 30 patients were operated on using intermittent aortic cross-clamping for the distal anastomoses. Cold cardioplegic myocardial protection has been used since June 1979.

Postoperative Follow-up

All patients were followed up at regular intervals at the outpatient clinic of our or the referring center; annual noninvasive evaluation was obtained in most cases. Only 2 patients living abroad were contacted by telephone. Late follow-up deaths were analyzed for cause and categorized into cardiac, neurological, and nonrelated. Considered as late cardiac events were recurrence of angina, signs of right or left heart failure, new myocardial infarctions, percutaneous transluminal coronary angioplasty, and coronary reoperations.

Late neurological events (TIA, RIND, stroke) were also analyzed in relation to preoperative variables, as well as the type of operation and the operated side. Strokes were considered major if a deficit persisted after more than 6 weeks.

Statistical Methods

Quantitative data are given as mean ± standard deviation. Univariate comparisons between groups were performed by the standard χ^2 test, the nonpaired t test, or the one-way analysis of variance whenever appropriate. Cumulative survival curves were made by means of the Kaplan-Meier product-limit method [21]. Independent predictors of early mortality (≤30 days) were identified by multiple logistic regression analysis [22]. For identification of independent determinants of long-term survival, the proportional hazard regression model introduced by Cox was used [23]. The relative risk of the risk factors was obtained by exponentiation of their coefficients obtained in the multivariate regression analysis. All computations were made using the BMDP statistical software package (BMDP release 1990).

Results

Operative Mortality and Morbidity

OPERATIVE MORTALITY. Eight patients died (3.5%) within 30 days after operation. The cause was cardiac in 4, including 2 patients who could not be weaned off bypass; 3 patients died of septicemia and multiorgan failure, and 1 neurologically determined death occurred. Hospital mortality did not change over the years (see Table 3), despite the increasing age of patients. Variables entered in a stepwise logistic regression to identify risk factors for early mortality were age, sex, NYHA class, degree of preoperative angina, preoperative left ventricular function graded as normal or moderate dysfunction versus severe dysfunction, preoperative number of infarcts, preoperative coronary angiography, presence of left main stem lesions, use of internal thoracic artery, occurrence of postoperative cardiac complications, redo CABG, other operative procedures, and bilateral HS extracranial disease.

Only the presence of left main stem lesions showed a significant association with hospital mortality: the proba-

Table 5. Cumulative Survival at 5, 10, 12, and 15 Years and Cumulative Event-Free Survival at 5, 10, and 12 Years Including Hospital Mortality and Morbidity

	% Survival ± SE		
Survival	5-year (n = 105)	10-year (n = 22)	12-year (n = 10) and 15-year (n = 2)[a]
Total survival	74.4 ± 3.3	53.7 ± 4.9	35.0 ± 6.6
Cardiac	86.0 ± 2.6	69.2 ± 4.7	47.4 ± 8.2
Neurological	97.2 ± 1.3	92.2 ± 3.7	87.8 ± 5.5
All events-free survival[b]	71.8 ± 3.5	43.8 ± 5.1	22.2 ± 6.1
	(n = 94)	(n = 17)	(n = 7)
Free of cardiac events	76.7 ± 3.3	53.0 ± 5.2	28.4 ± 7.0
	(n = 97)	(n = 18)	(n = 8)
Free of neurological events	92.8 ± 2.1	84.4 ± 4.3	80.2 ± 5.8
	(n = 102)	(n = 21)	(n = 9)

[a] Only 12-year for event-free survival. [b] Events are marked angina, myocardial infarction, reoperation, heart failure or cardiac death, and reversible ischemic neurologic deficits, strokes, or neurological death.

SE = standard error.

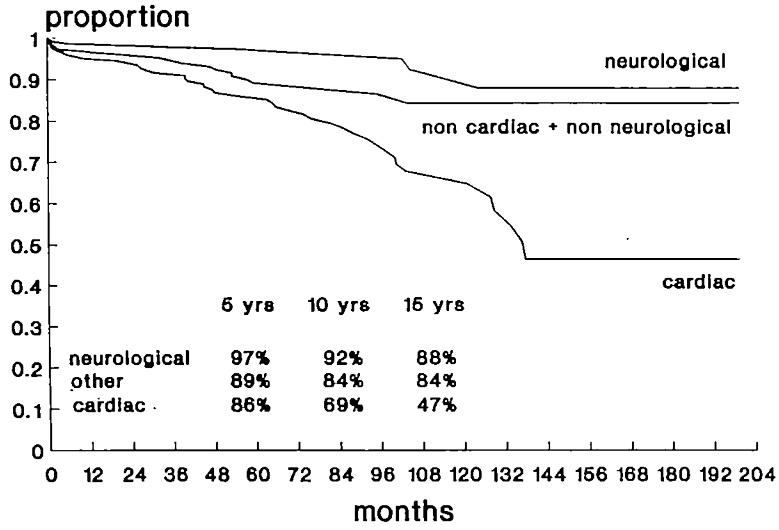

Fig 2. Late cardiac, neurological, and noncardiac nonneurological mortality: survival including hospital mortality in 230 synchronous operations (at 5 years n = 105, at 10 years n = 22, at 12 years n = 10, and at 15 years n = 2).

bility of dying in the hospital was 1.2% in the absence ($p < 0.0001$) and 9.1% in the presence ($p = 0.013$) of a left main stem lesion (log regression coefficient and standard error of presence of left main stem lesion, 2.079 and 0.827; constant and standard error in this model, −4.382 and 0.708).

OPERATIVE MORBIDITY. Perioperative myocardial infarction occurred in 4 patients. Three patients had a period of ventricular tachyarrhythmias not related to permanent new electrocardiographic changes. Five patients had to be treated for temporary low cardiac output; an intraaortic balloon pump was used in only 1 patient. Two patients needed prolonged respiratory support, and 2 patients suffered delayed sternal healing.

The predominant postoperative complication was neurological. Twenty new neurological events occurred (8.7%): 6 were TIAs, 3 related and 3 nonrelated to the operative side(s); 7 were RINDs; and 7 were major strokes. Two of these seven RINDs and five major strokes were related to the operated side(s) (3%). Variables entered in a stepwise logistic regression to identify risk factors for postoperative neurological complications were age, sex, preoperative NYHA class, preoperative neurological status (asymptomatic versus TIAs versus RIND or stroke), preoperative left ventricular function, presence of severe or unstable angina pectoris, other associated cardiac or noncardiac procedures, redo CABG, HS bilateral disease, and performance of bilateral extracranial operation (either bilateral carotid endarterectomy or combinations of innominate artery or common carotid artery and contralateral carotid bifurcation endarterectomy).

Postoperative neurological complications were grouped as all neurological complications (n = 20), severe neurological deficits only (n = 14), and operative-side-related severe neurological deficits (n = 7) (Table 4). The constant risk of a postoperative neurological event was slightly increased (1.4 times) by the presence of preoperative TIAs or amaurosis fugax, but was increased significantly (3.9 times) by the presence of preoperative RINDs or strokes ($p = 0.046$). The presence of preoperative severe left ventricular dysfunction increased the risk 2.44 times, but was marginally significant ($p = 0.074$).

Although marginally significant, the only factor increasing the risk for *severe* postoperative neurological deficits was the presence of bilateral HS lesions, which increased the risk 2.7 times ($p = 0.089$); the performance of bilateral operation, however, was not related to this event ($p = 0.49$).

No single factor could be found that significantly influenced the event rate when only operative-side-related severe neurological deficits were analyzed.

Late Mortality and Morbidity

LATE MORTALITY. Sixty-six deaths occurred in the follow-up period between 30 days and 16.3 years after operation: 41 cardiac, 7 neurological, and 18 other nonrelated deaths. The causes of late cardiac death were related

Table 6. Multivariate Prediction (proportional hazards model) of Late Cardiac Mortality (>30 days) in 226 Cardiac Hospital Survivors[a]

Risk Factors[b]	Regression Coefficient	Standard Error	p Value
Presence of severe LV dysfunction[b]	1.638	0.374	<0.0001
Reoperative CABG	1.366	0.638	0.07
Age per year	0.048	0.025	0.05
Use of ITA	−1.225	0.781	0.07
Presence of preoperative infarction	0.643	0.422	0.12

[a] Global χ^2 of final Cox model = 47.66 ($p < 0.0001$). [b] See text.

CABG = coronary artery bypass grafting; ITA = internal thoracic artery; LV = left ventricle.

Table 7. Multivariate Prediction (proportional hazards model) of Total Late Mortality (>30 days) in 222 Hospital Survivors[a]

Risk Factors[b]	Regression Coefficient	Standard Error	p Value
Presence of severe LV dysfunction[b]	0.948	0.276	0.0006
Preop infarction	0.595	0.305	0.0459
Age (per year)	0.046	0.019	0.0141
Use of ITA	−0.758	0.495	0.0975

[a] Global χ^2 of final Cox model = 34.64 ($p < 0.0001$). [b] See text.

ITA = internal thoracic artery; LV = left ventricular.

to recurrent angina or new or recurrent myocardial infarction (n = 18), sudden death (n = 9), and heart failure (n = 14). Late cardiac survival at 5, 10, and 15 years, including hospital mortality, is mentioned in Table 5 and illustrated in Figure 2.

Multivariate stepwise regression analysis was performed of the determinants of total and cardiac late mortality (Tables 6, 7). Variables analyzed were age; sex; NYHA class II, III, and IV; two- or three-vessel disease; preoperative myocardial infarction; severe left ventricular dysfunction; use of internal thoracic artery; other synchronous procedures; redo CABG; severe bilateral HS extracranial lesions; and bilateral extracranial operation. Late cardiac death was associated with the presence of severe preoperative left ventricular dysfunction ($p < 0.0001$) and with reoperation ($p = 0.07$); the probability of late cardiac death was increased fivefold by a poor left ventricle and fourfold in reoperative CABG. Age as well as the presence of preoperative infarction(s) increased the risk, respectively, by a factor of 1.05 per year and of 1.9; the use of an internal thoracic artery decreased the risk of dying by a factor of 0.3.

The seven late neurological deaths were caused in 2 patients by a related stroke, in 2 by a nonrelated stroke, and in 3 by cerebral hemorrhage (most of the patients were on a life-long regimen of oral angicoagulants) (see Fig 2). At multivariate stepwise regression analysis, the variables analyzed were age, sex, NYHA class, preoperative presence of neurological symptoms, presence of bilateral HS lesions, performance of bilateral operation, and presence of postoperative neurological complications. No specific preoperative or postoperative neurological variable appeared to be significantly associated with late neurological death.

LATE MORBIDITY. Mild angina recurred in 47 patients and severe angina in 7; 22 patients had signs of right or left heart failure, 8 had one new or recurrent myocardial infarction, and 1 patient had two episodes of myocardial infarction. Late percutaneous transluminal coronary angioplasty was performed in 6 and reoperative CABG in 11 patients. Two of these patients were submitted to synchronous reoperative CABG and carotid endarterectomy of the side not operated on the first time.

To analyze cardiac event-free survival, 69 late cardiac events including cardiac mortality were censored as first cardiac events. The 5-, 10-, and 12-year cardiac event-free survival rates are given in Table 5 and presented in Figure 3.

Of the late neurological events, four were related and ten nonrelated TIAs; these 14 TIAs were not included in the analysis of the event-free curves. Two hemispheric RINDs and two strokes related to the operated side occurred during the follow-up; 2 RINDs, 5 hemispheric strokes, and 2 vertebrobasilar strokes were not related. Eighteen neurological events—defined as RINDS, strokes, or neurological deaths—were censored as the first neurological event during the follow-up. The respective 5-, 10-, and 12-year neurological event-free survival

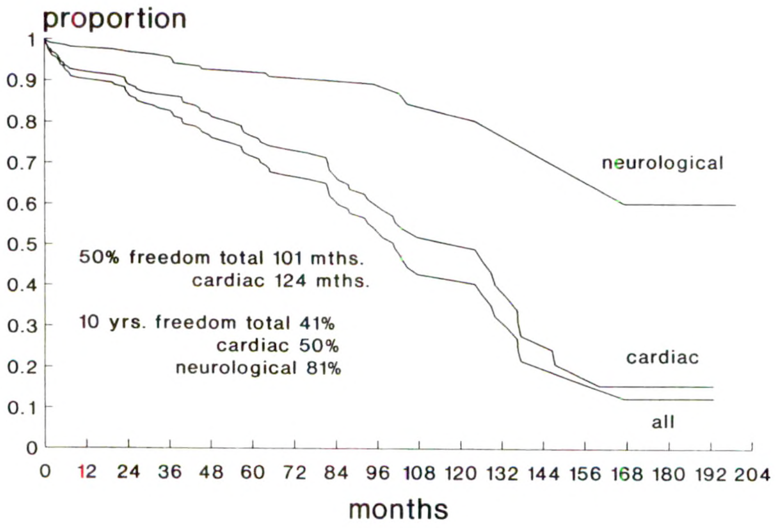

Fig 3. Total, cardiac, and neurological event-free survival in 230 patients undergoing synchronous operations (for each curve n at 5, 10, and 12 years see Table 6).

rates and survival curves are given in Table 6 and Figure 3.

When all neurological and cardiac events as well as deaths are included in a disease-related event-free survival curve, only 12.7% of the patients were completely event-free at 15 years.

Comment

The reliability of noninvasive assessment of HS extracranial disease has been well documented. The OPG-Gee has been a reliable and simple screening test in patients with bruits and has an acceptable predictive value for detecting serious lesions [14]. Screening patients scheduled for open heart operations by submitting them to the OPG-Gee test [24] showed that using the test only for patients with extracranial bruits or neurological symptoms will allow the detection of almost all patients with an HS stenosis as documented by routine angiography. Balderman and associates [25] came to similar conclusions in a series of 500 patients.

Since 1981, duplex scanning has demonstrated its reliability in the detection of HS extracranial lesions defined as either 80% or greater stenosis or occlusions [7] or even as subgroups of 65% to 90%, 90% to 99% stenosis, and occlusions [15, 17]. In prospective studies on the natural history of asymptomatic carotid artery disease it has now been well documented, in patients with bruits [6, 19, 26, 27] as well as with asymptomatic stenosis [27], that high-grade asymptomatic stenosis of more than 80%, or more than 90%, induces a marked increase in stroke rates of up to 5% in the first year after diagnosis, many without preceding TIAs [6, 26]. Almost from the outset, we have focused on HS lesions even in *symptomatic* patients. Indeed, we have used oral warfarin sodium in combination with dipyridamole, 150 mg twice a day, as standard postoperative treatment in CABG patients; we assumed that this treatment would also be efficacious in the prevention of postoperative neurological events in the non-HS lesions. At present, we rely on the initial screening of patients with a history of symptoms or bruits with OPG Gee or duplex scanning, or both.

We have included, in our selection of patients with unilateral carotid disease, the concept of presumed stroke risk in the event of progression to occlusion. We have found [18, 19] that, in most patients in whom a carotid stenosis progressed to a HS lesion at follow-up, the collateral ophthalmic artery pressure did not change on the side with progression. This shows that the collateral supply does not improve with time or with progression of stenosis, which indicates that the collateral capacity of the circle of Willis—as investigated by carotid compression tests during OPG or during electroencephalography—will provide valuable information in each *individual* patient regarding his or her risk in the event of occlusion. Incorporation of this risk into patient selection in the presence of asymptomatic HS lesions seems to be appropriate. Only recently, other authors [7, 28, 29] have referred to the presence of a hidden "increased stroke risk" in patients with severe carotid stenosis, as unmasked during compression test or shown by the absence of cerebral perfusion reserve. We have noticed only two reversible strokes in more than 11,000 carotid compression tests and therefore consider their risk clinically acceptable.

Table 8. Risk of Related Neurological Complications in Patients With Asymptomatic Unilateral Hemodynamic Carotid Stenosis and Synchronous Operations (n = 73)

Compression Intolerance[a]	No. of Patients	Shunt Used	Neurological Complications
Present	28	5	1 related TIA, 1 related stroke
Absent	36	1	1 nonrelated TIA, 1 nonrelated RIND
Not tested	9	0	0

[a] Collateral ophthalmic artery pressure ≤40 mm Hg and/or compression intolerance at preop electroencephalography.

RIND = reversible ischemic neurologic deficit; TIA = transient ischemic attack.

In our subgroup of patients with asymptomatic unilateral HS carotid disease (n = 73), one related and one nonrelated TIA occurred, and one related stroke and one nonrelated RIND occurred. However, both of the related complications occurred in the subgroup of 28 patients who did not tolerate compression of the stenotic artery to be operated on. We believed that these patients had a strong indication for synchronous operation. Indeed, in the event of less severe cardiac disease, their carotid operation would have been carried out first; in any case, if not operated on synchronously, their CABG would have been shortly followed by the carotid endarterectomy (Table 8) with an approximately equal stroke risk. This individual patient-related stroke risk has not been considered in the one available prospectively randomized trial of synchronous versus staged operation in patients with CABG and asymptomatic severe unilateral carotid disease [1, 9, 30].

Many prospective studies have evaluated the stroke risk in CABG patients in the presence of extracranial bruits or documented evidence of extracranial lesions [2, 3, 4, 31, 32]. Overall, the stroke rate in this population was approximately 3% to 4%. An increased risk was documented when the carotid obstruction was hemodynamically significant [33]. In addition, the patients with documented but nonoperated carotid artery stenosis showed a 4% stroke rate per annum during the first 4 years after their isolated CABG [34].

The recent follow-up study by Brener and co-workers [9] showed that the presence of carotid stenoses (graded as ≥50%) in CABG patients increased the overall TIA and stroke rate from 1.9% to 9.2%; the incidence of postoperative deficits was also higher in patients with inoperable occluded carotid arteries as compared with patients with operable lesions (15.6% versus 7.4%). Brener and co-workers observed the highest complication rate in patients with unilateral occlusion and controlateral stenosis. They also noticed that patients with serious carotid disease showed a threefold higher cardiac operative mortality than patients without this pathology. Barnes [33] reviewed all patients with asymptomatic carotid artery disease and coronary revascularization submitted to staged procedures—in whom a carotid endarterectomy was carried out as a first operation—versus synchronous operations. In 1,483 collected patients the overall perioperative stroke risk was 2.9%; it was 3.1% in staged carotid first and 2.8% in synchronous operations. However, the perioperative myocardial infarction rate was significantly lower in synchronous operations versus staged procedures (3.8% versus 11.8%). The operative mortality also was lower in synchronous operations (4.7%) versus staged (11.1%). Hornig and colleagues [32], in their recent overview of 1,023 patients who underwent synchronous operation, mention an incidence of neurological deficits of 3.8% and a mortality of 5.4%.

In patients with bilateral HS carotid disease—with or without symptoms—the risk of cerebral complication is increased [9, 35–37]. Hertzer and associates [38] documented that the risk of carotid endarterectomy was related to the severity of the contralateral lesion and was higher in patients with contralateral occlusion. Barnes and co-workers [31] observed a far higher complication rate in patients with documented bilateral extracranial disease as compared with those with unilateral lesions when only CABG was performed.

In the presence of bilateral HS lesions, many authors [1, 5, 12] advocate treatment of at least one carotid artery as a staged procedure before the coronary revascularization or before the combined procedure including the other side. However, this approach incorporates all the risks of a staged procedure (carotid first). We believe that in patients with severe cardiac disease, both carotid arteries should be considered for synchronous operation if both hemispheres are considered to be prone to stroke. However, in the event that carotid compression is well tolerated, either the side of the most severe stenosis or the symptomatic side can be chosen for the synchronous procedure.

Considering the documented risks of the mere presence of extensive cerebrovascular disease, our overall operative neurological event rate of 8.7% and our rate of related severe neurological events of 3% appear to be acceptable.

In our analysis of risk factors for all operative neurological complications, the preoperative presence of severe neurological accidents—with or without residual deficits—and preoperative severe left ventricular dysfunction were shown to be significantly associated with postoperative neurological events. Gardner and associates [10] also noticed this association, in addition to the impact of age and extracorporeal perfusion time. In our analysis, perfusion time was not analyzed. Age, however, did not appear to have a significant association. When only severe operative neurological events are taken into consideration, the presence of bilateral HS carotid disease, and not the performance of a bilateral carotid endarterectomy, was the single related factor.

Our operative mortality (3.5%) is within the limits of the overall published series, notwithstanding the presence of very extensive disease. In our analysis only the presence of left main stem lesions showed a significant association with hospital mortality. This has also been documented by Gardner and associates [10] and Schwartz and coworkers [39]. The impact of left main stem lesion on operative mortality in isolated CABG has been documented earlier [40].

Few data are available regarding the long-term survival of patients who undergo synchronous operation. Hertzer and associates [1] indicated after a higher first-year mortality, an almost parallel survival of patients up to 5 years as compared with a control group with only CABG. In the present study, the survival rates are certainly worse than the overall survival rates in patients with extensive coronary revascularization but without associated carotid artery disease [41]; however, the mean age in the latter series was 51 years [41] and is therefore 10 years less than in the present synchronous operation series. The late outcome in our patients undergoing synchronous operation was determined by the cardiac prognosis; late cardiac death was strongly associated with the presence of severe preoperative left ventricular dysfunction and with reoperative CABG. It has been well documented [42, 43] that both these determinants have a comparable impact on patient survival in isolated CABG. The same is true for the impact of the presence of preoperative infarctions and age on survival [44].

The favorable influence on the long-term outcome of the use of the internal thoracic artery has been documented in many series with isolated CABG. We have only used an internal thoracic artery from 1984 in this type of synchronous operations, which probably explains the relatively weak beneficial influence found in our analysis. The influence will probably become more evident because the major late events are mainly related to recurrence or progression of coronary artery disease.

The impact of severe left ventricular dysfunction on late outcome certainly requires unequivocal indications for synchronous operation in this subgroup of patients.

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DISCUSSION

DR JOHN B. FLEGE, JR (Cincinnati, OH): Please explain the sequencing of your operation and whether or not you use carotid shunting on either side when you do the bilateral carotid endarterectomies.

DR VERMEULEN: Regarding the sequence of the operation, we first do the carotid procedure. Sometimes, in unstable patients or in reoperations, we would open the chest first, then do the carotid procedure before we cannulate. We use a shunt only on indication, even in bilateral operations, because we have monitored for many years the operative occlusion tolerance with an automatic electroencephalogram analyzer, a sophisticated device that has been developed in our institution; in recent years we also have used operative transcranial Doppler monitoring.

In bilateral carotid operations, we would operate first on the side with occlusion tolerance at the preoperative testing; intraoperatively this is tested again. If occlusion is not tolerated on either side, we would choose the side with the highest stump pressure to be operated on first, and with a shunt. The occlusion intolerance of the second side is then tested again; if needed, a second side shunting is used.

Only recently, in 2 patients in whom the anatomical approach was difficult and in whom a shunt was indicated, we elected to do the carotid endarterectomy on hypothermic cardiopulmonary bypass. Rather than using a shunt, we used hypothermia for brain protection.

DR ALEXANDER S. GEHA (Cleveland, OH): Otherwise you do it first?

DR VERMEULEN: We do it first.

DR DONALD R. KAHN (Birmingham, AL): We have had an experience similar to that reported in this excellent paper. We have performed 140 combined procedures over the past 10 years, with the indication that the patient had a 90% or greater obstruction in the carotid artery. Our hospital mortality rate was 3½%, very similar to that presented here. Our 10-year survival has been better, similar to the survival of the cardiac procedure itself.

DR JOSEPH M. CRAVER (Atlanta, GA): My colleagues and I have been interested in patients with combined disease for quite a period of time, and earlier we were operating on asymptomatic lesions with coronary bypass at the same time. I have abandoned that in the last 5 years and have believed that asymptomatic patients do as well, and the incidence of postoperative stroke really does not relate to the side with the particular disease as you demonstrated in your data as well.

More recently we have not considered even studying those patients who were not symptomatic. Yet, if they are symptomatic, we proceed by referring them to the vascular surgeons for study and an operation on the symptomatic side under local anesthesia. The cardiac operation is then performed 2 or 3 days later. With this practice, over the last 3 years we have had no strokes at all in this population and no cerebral events related in the subsequent open heart procedures.

I would submit that for your consideration and comment.

DR VERMEULEN: Well, I am fully aware that there are different philosophies leading to acceptable results, such as operating under cervical block. That is one technique we have not explored. But in my early experience I have not been very impressed by operations on the carotid artery under local anaesthesia. I experienced that the patients sometimes get very excited, nervous, or hypertensive, especially when they do get symptoms while the occlusion is tested. Then the patients get extremely excited and may disrupt your whole operative set-up and disturb the operation as you have planned it. So that is why we abandoned operating under local anesthesia. But of course if your results prove or could show that the incidence of neurological defects is less, it is of course worthwhile to evaluate it again in this complex type of patients.

Adjuvant Treatment Using Transfer Factor for Bronchogenic Carcinoma: Long-Term Follow-up

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Transfer factor, a dialyzable lymphocyte extract that may act as an immune stimulator by transferring antigen-specific immunity between genetically dissimilar individuals, was administered in a prospective, randomized study to patients with non–small cell bronchogenic carcinoma. Between 1976 and 1982, 63 patients who underwent pulmonary resection, mediastinal lymph node dissection, and, when indicated by the presence of mediastinal lymph node involvement, mediastinal irradiation were randomized into two groups. Group 1 (n = 28) received 1 mL of pooled transfer factor at 3-month intervals after operation; group 2 (n = 35) served as controls and received saline solution. There were no statistically significant differences between the two groups with respect to age, sex, tumor histology, stage of disease, or extent of resection. One patient was lost to follow-up at 96 months; follow-up was complete in all others through July 1990. In patients receiving transfer factor, the 2-, 5-, and 10-year survival rates were 82%, 64%, and 43% respectively, whereas in controls they were 63%, 43%, and 23%. Survival in patients receiving transfer factor was consistently better than in those receiving placebo. Furthermore, survival in patients receiving transfer factor was greater at all stages of disease for both adenocarcinoma and squamous cell carcinoma. Although these long-term results were not statistically significant using survival analysis with covariates ($p = 0.08$), they confirm our previously reported short-term findings suggesting that administration of transfer factor, either through nonspecific immune stimulation, enhancement of cell-mediated immunity, or an as yet undefined mechanism, can improve survival in patients with bronchogenic carcinoma.

(Ann Thorac Surg 1992;53:391–6)

Bronchogenic carcinoma remains the most common form of malignant neoplasm—other than skin cancer—in this country and continues to be the leading cause of cancer deaths. Approximately 50% of patients newly diagnosed as having bronchogenic carcinoma are determined to have extrathoracic disease at the time of diagnosis and are therefore considered incurable. Although surgical resection remains the only potential form of cure for the remaining patients, even for those with limited stage I disease, cure cannot be accomplished in 30% to 40% [1]. Adjuvant trials of chemotherapy and radiotherapy have been undertaken with conflicting, frequently unrewarding results [2].

Immunotherapy, the concept of using the patient's own immune system against the tumor, has been applied to bronchogenic carcinoma in several forms including administration of Bacille bilié de Calmette-Guérin [3–9], immunization with tumor extracts [10, 11], use of Levamisole (Janssen Pharmaceuticals, Piscataway, NJ) [12, 13], and administration of transfer factor, a low-molecular weight lymphocyte extract that can transfer antigen-specific, cell-mediated immunity [14–20]. In 1984 we [14] reported early results of a randomized, prospective study using transfer factor in patients with resectable disease. Our results suggested that transfer factor had significant effects on the prolongation of life. We now report follow-up of these patients up to 14 years.

Material and Methods

Patients

Between 1976 and 1982, 63 patients undergoing pulmonary resection for lung cancer were entered into a prospective, randomized study to determine whether transfer factor affected survival in patients with non–small cell bronchogenic carcinoma. Before operation, all patients were considered to have curable lesions, ie, there was no evidence of distant metastases or mediastinal lymphadenopathy as assessed by tomography, computed tomography, anterior mediastinotomy, or mediastinoscopy. No patients who had received preoperative radiotherapy or chemotherapy or who had small cell carcinoma were included in this study. The extent of pulmonary resection was determined at the time of operation according to the size and extent of the tumor; wedge and segmental resections were not performed. Mediastinal lymph node dissection, including removal of the superior mediastinal, subaortic, subcarinal, and paraesophageal nodes, was performed in all patients. Resection was considered curative if all gross tumor was removed; only patients in this category were eligible for the study.

Postoperative adjuvant radiation therapy was given to all patients found to have mediastinal metastases. This consisted of 50 to 60 Gy administered in daily doses of 2 Gy over 5 to 6 weeks.

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Patients were staged according to criteria established by the American Joint Committee for Cancer Staging and End-Results Reporting [21] based on the operative and pathological findings. They were prospectively randomized into two groups: group 1 (n = 28) received pooled transfer factor whereas group 2 (n = 35) received placebo. Beginning 1 month postoperatively, or after radiotherapy, patients in group 1 received 1 mL of transfer factor intramuscularly. Subsequent doses were administered at 3-month intervals until the end of the study in July 1986. Patients in group 2 were given saline solution using the same technique and dosing interval. Patients were blinded as to which arm of the study they were assigned.

Patients were followed up in the Thoracic Surgery Clinic at the University of Michigan at 3-month intervals for the first 3 years after operation, at 6-month intervals for the next 3 years, and yearly thereafter. Additional follow-up and survival were determined by phone contact with the patient or his or her personal physician.

Transfer Factor

Two pools of transfer factor were extracted from the peripheral blood lymphocytes of normal individuals. The first, prepared in 1976, was from Red Cross volunteers; the second, prepared in 1980, was from healthy medical students. Peripheral venous blood was drawn into an acid-citrate-dextrose pack (450 mL) and washed twice with sterile 0.87% ammonium chloride and once with Ringer's solution. The cell suspensions were centrifuged to obtain a leukocyte pellet measuring 10 to 12 mL and containing approximately 10^9 leukocytes and 1 to 6 × 10^8 lymphocytes. These were stored at −70°C until they could be combined into one pool. The cell suspensions were then thawed, combined, and sonicated for 5 minutes using a Bronson sonicator. Transfer factor was extracted by vacuum dialysis for 18 hours using a Prosifill Unit. The dialysates were filtered through a 22-μm filter, cultured for bacteria, and assayed for endotoxin and hepatitis B antigen. Transfer factor obtained from 10^8 peripheral blood lymphocytes was reconstituted in 1 mL of 0.85% sodium chloride before administration.

Statistical Analysis

Differences between groups 1 and 2 with respect to sex, tumor histology, type of operation, and tumor stage were analyzed by the χ^2 method. For age, Student's t test was used. Survival was analyzed using the Kaplan-Meier life-table method [22] and the Cox proportional hazards model with covariates [23]. A result with a p value less than 0.05 was considered statistically significant.

Results

Patients

The profiles of the two groups of patients are shown in Table 1. There were no statistically significant differences between the two groups with respect to age, sex, extent of resection, stage of disease, or tumor histology.

Table 1. Characteristics of Patients in Transfer Factor and Control Groups

Characteristic	Group 1 (n = 28)	Group 2 (n = 35)
Mean age (y)	59	61
Sex		
Male	16	26
Female	12	9
Histology		
Adenocarcinoma	11	21
Squamous carcinoma	17	14
Stage		
I	17	23
II	6	5
III	5	7

Overall Survival

The overall survival curves for the two groups of patients are shown in Figure 1. The 2-, 5-, and 10-year survival rates for patients receiving transfer factor are 82%, 64%, 43%, respectively. Patients receiving placebo had survival rates of 63%, 43%, and 23% at the same time intervals. Patients receiving transfer factor had consistently better survival than those receiving placebo, although these differences did not attain statistical significance, either for treatment effects only ($p = 0.13$) or when the covariates of age, sex, pathology, and stage were included ($p = 0.08$).

Effect of Transfer Factor Relative to Stage of Disease

Survival of patients with stage I disease is presented in Figure 2. Patients who received transfer factor had better survival than those who received placebo, but these differences were not statistically significant. For patients with stage I disease, the 5- and 10-year survival rates for those receiving transfer factor were 76% and 53% respectively, whereas for those receiving placebo they were 65% and 31%.

Patients with stages II and III disease extending beyond the lung had significantly worse survival rates than those with limited stage I disease irrespective of treatment with transfer factor ($p = 0.0007$). Survival data for these patients are presented in Figure 3. Patients receiving transfer factor survived better than those receiving placebo but, again, these differences were not statistically significant. The mean survival for patients with stage II disease was 60 months in group 1 (treatment) but only 24 months in group 2 (controls). Among patients with stage III disease, 2 of the 5 who received transfer factor survived for longer than 10 years whereas all patients who received placebo were dead by 40 months.

Effect of Transfer Factor Relative to Tumor Histology

Survival data are analyzed with respect to tumor histology and are shown in Figures 4 and 5. Patients who received transfer factor survived better than controls both in cases of adenocarcinoma and of squamous cell carcinoma, but these differences were not statistically significant. Statistical analysis of survival combining tumor histology and

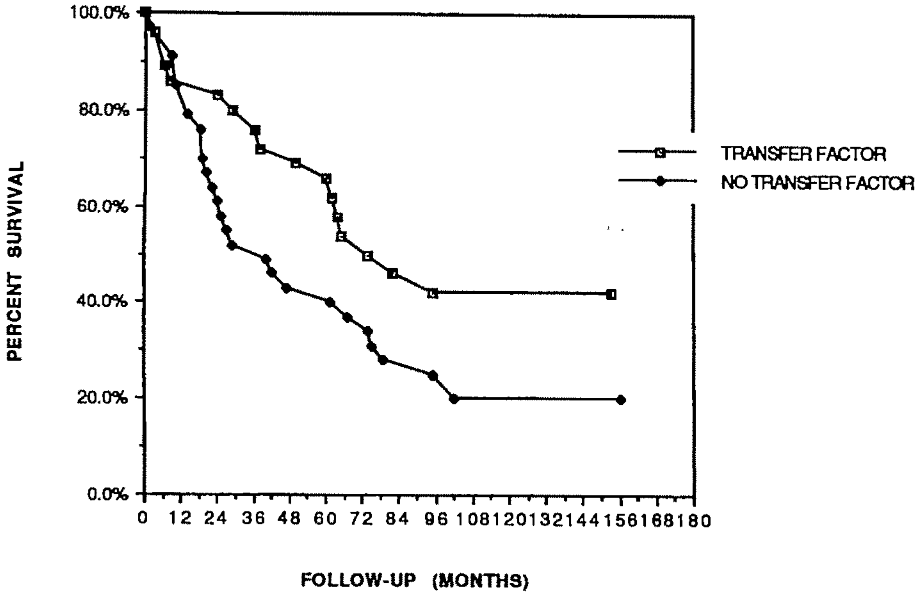

Fig 1. Effect of transfer factor on survival for all patients.

stage of disease was not performed due to the small number of patients in each subgroup.

Comment

In spite of great advances in many areas of medicine, the treatment of bronchogenic carcinoma, the leading cause of cancer deaths, has progressed little over the last several decades. Surgical resection, which offers the only chance of cure, is appropriate for only a minority of the patients afflicted with this disease and provides a cure for only a few of those to whom it is applied. To improve upon these results adjuvant forms of treatment, including chemotherapy, radiation and immunotherapy, have been added to surgical resection.

Immunotherapy, using the patient's own immune system against a tumor, is an inherently attractive concept. It should provide the systemic tumoricidal effects of chemotherapy with the ability to deal with a small but widely dispersed tumor burden. It has the potential of being long-lasting, while being devoid of many of the toxic and immunocompromising effects of conventional chemotherapeutic agents.

Immunotherapy has been applied to bronchogenic carcinoma in several forms. Bacille bilié de Calmette-Guérin, a nonspecific immune stimulator that has been associated with some promising results in the treatment of melanoma, has been given intradermally, intralesionally, intrapleurally, and orally in cases of bronchogenic carcinoma [3-9]. The results of these studies have been inconclusive with some studies demonstrating benefits after Bacille bilié de Calmette-Guérin administration [4, 9] and others failing to show improvement in survival [5-8]. *Corynebacterium parvum*, another nonspecific immune

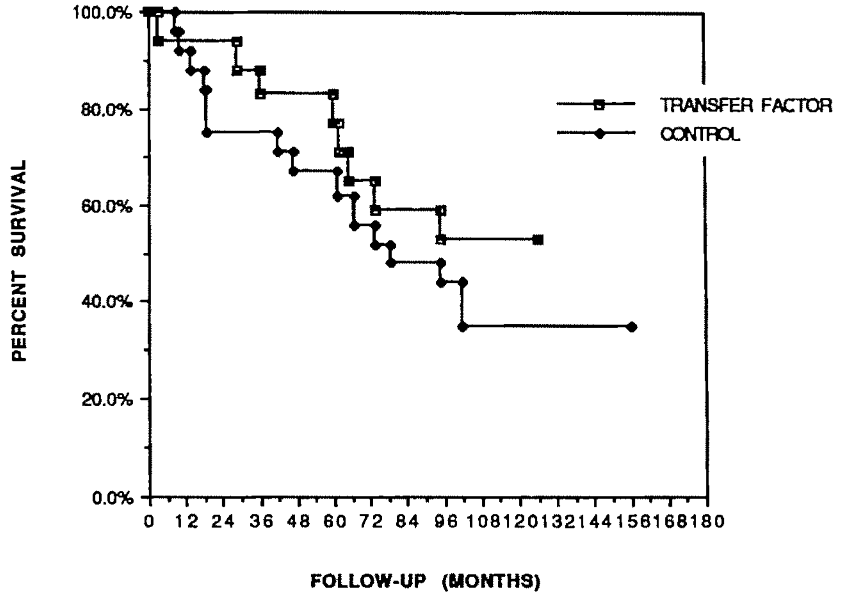

Fig 2. Effect of transfer factor on survival in patients with stage I disease.

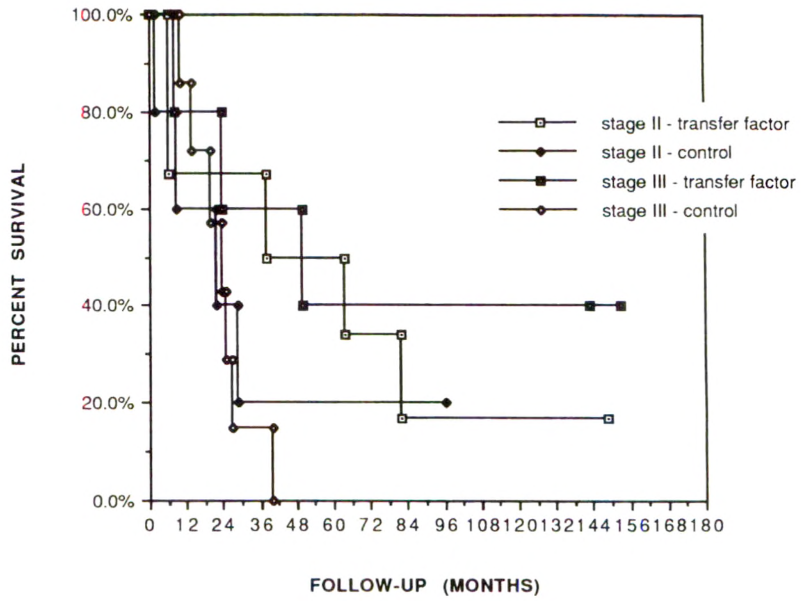

Fig 3. Effect of transfer factor on survival in patients with stage II and III disease.

stimulator of bacterial origin, had a negative effect on survival when used intrapleurally [24]. Another form of nonspecific immune stimulation involves the use of Levamisole. Previously used as an antihelminthic agent, this drug has been widely applied as an adjuvant in the treatment of colon carcinoma. Believed to be an immune stimulator, it has been applied to the treatment of bronchogenic carcinoma with conflicting results [12, 13].

Studies by Stewart and associates [10] and Takita and co-workers [11] suggest improved survival after active immunization, although their results are difficult to interpret due to selection of controls. Recent advances in immunobiology and improved understanding of immune modifiers, including interleukin-2, tumor necrosis factor-alpha, and the interferons, have led investigators such as Rosenberg and others to apply adoptive immunotherapy in both laboratory studies and clinical trials [25–27]. These trials have involved administration of interleukin-2 with or without lymphocyte-activated killer cells to patients with advanced cancers.

An additional form of immunotherapy involves the use of transfer factor. In 1949 Lawrence [28] demonstrated the adaptive transfer of cell-mediated immunity through a dialyzable lymphocyte extract later called transfer factor. Additional work by Fudenberg and Fudenberg [16] has shown Lawrence's dialyzable leukocyte extract to contain at least 200 moieties ranging in molecular weight from 1000 to 20,000 daltons and the antigen-specific transfer factor to consist of an RNA-polypeptide complex with a molecular weight of approximately 3,500. Transfer factor's mechanism of action is unclear, but it has been hypothesized that transfer factor forms part of the T-cell receptor [6, 29] and may be transferred to immunologically uncommitted T-lymphocytes, thus rendering them antigen-specific

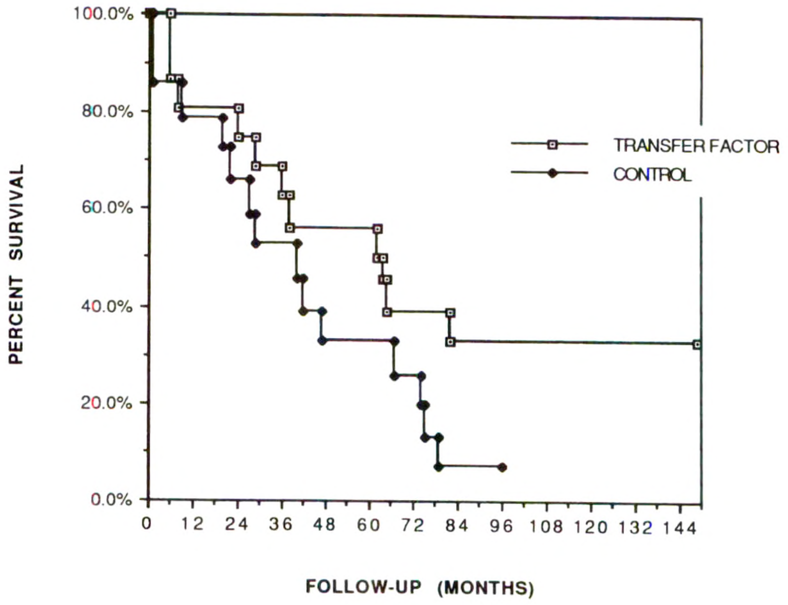

Fig 4. Effect of transfer factor on survival in patients with squamous cell carcinoma.

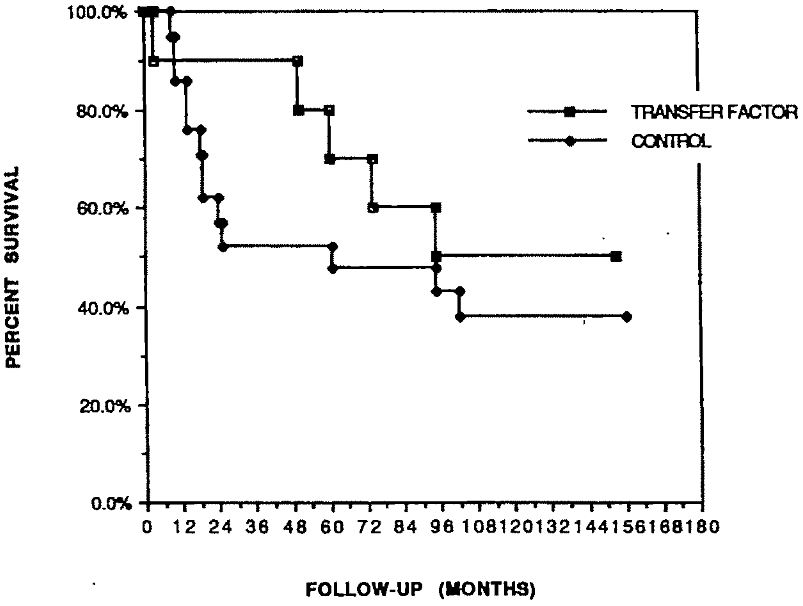

Fig 5. Effect of transfer factor on survival in patients with adenocarcinoma.

and responsive. An additional proposed mechanism involves binding of the RNA moiety to complementary DNA on the cell surface with incorporation of the transfer factor into the recipient cell [16]. Regardless of its mechanism of action, transfer factor has been useful in the treatment of certain immune deficiency states such as mucocutaneous candidiasis and Wiskott-Aldrich syndrome [16, 29], both diseases of the cell-mediated immune response.

In addition to its uses in the above-mentioned immune deficiency conditions, transfer factor has been used in the treatment of several malignancies including osteogenic sarcoma, mycosis fungoides, malignant melanoma, and carcinomas of the breast, lung, and kidney [6, 14]. Although results have been variable, some reports have suggested improved survival after treatment with transfer factor [18, 20]. In addition to its use in our previous report [14], transfer factor has been used in the treatment of bronchogenic carcinoma by Fujisawa and associates [15]. Their results indicated that use of transfer factor resulted in improved survival in patients with completely resected stage I or II disease but not in those with stage III or IV or in those with incompletely resected disease. Their results are complicated by the fact that all patients received adjuvant chemotherapy, including methotrexate, vincristine, mitomycin C, 5-fluorouracil, cyclophosphamide, and a nitrosourea, which may have resulted in substantial immune suppression.

There are several potential ways that transfer factor may enhance survival in bronchogenic carcinoma. Because it is likely that defects in the immune response may be, in part, responsible for the progression of lung cancer, and there is additional evidence that bronchogenic carcinoma may profoundly suppress the immune system [1], it follows that reconstitution of immune function may enhance survival. It is possible that transfer factor, either through intrinsic, nonspecific stimulation of the immune system or through adjuvantlike properties of the transfer factor preparation, could reverse the immune-suppressing properties of the tumor. There are few data to support this, however, as neither our previous report nor that of Fujisawa and associates provided data to support a general increase in cell-mediated immunity after administration of transfer factor.

An alternative proposal is that transfer factor provides antigen-specific improvement in immune function. Fujisawa and associates, who used household contacts for transfer factor preparation, noted that 30% of donors demonstrated a positive response to tumor cell extracts when tested in vitro. Fudenberg and Fudenberg [16] have emphasized the need for appropriate transfer factor donors to gain maximum benefit in transferring cell-mediated immunity and delayed hypersensitivity. Although it has not been proved, it seems reasonable that this should extend to antitumor activity as well.

In conclusion, although the effects of immunotherapy are unproven, there is reasonable evidence that enhancement of immune function may improve survival. The data presented in this report describe a prospective study in which patients with bronchogenic carcinoma were randomized to receive transfer factor or placebo. Survival in patients receiving transfer factor was consistently better than in those receiving placebo. We believe that these data add additional weight to the argument that immunotherapy has potential benefits in the treatment of bronchogenic carcinoma and that these methods should be further investigated.

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DISCUSSION

DR HARVEY I. PASS (Bethesda, MD): What is transfer factor? Is it interleukin-2? Is it commercially available? Is it available as a recombinant form, and what is the toxicity of giving it?

DR WHYTE: There is not much work being done currently on transfer factor. Much of the work that was done on this substance was done in the late 1970s and early 1980s, primarily by two groups, one in New York and one in South Carolina. Recently more work has been done on the better characterized cytokines: the interleukins, interferon, and tumor necrosis factor. However, we do know that transfer factor is a rather heterogeneous group of substances, which are RNA-polypeptide complexes that have a molecular weight of approximately 3,500 to 10,000. I am not aware that it is commercially available at this time. It has minimal toxicities. One of the concerns, obviously, is that in giving this substance, you may be able to transmit viral vectors or human immunodeficiency virus. This has been very difficult for me to find out because very few people work in this area at the present time. Because of this we do not plan further studies on this substance; however, we do feel that there is some evidence that it does improve survival in these patients.

DR JOHN P. CLARKE (Virginia Beach, VA): I just wondered about your 31% 10-year survival rate in the stage I control group. That seems a bit low. Is there any comment on that?

DR WHYTE: I agree with you that it is somewhat low in that you would expect the survival rate somewhere in the order of 60% or so. I do not have a good explanation as to why this group had a lower than expected survival rate.

DR RICHARD F. HEITMILLER (Baltimore, MD): Dr Whyte, I enjoyed your presentation. In addition to any survival differences that you noted in the two treatment groups, did you notice any differences in pattern of disease recurrence?

DR WHYTE: This was not specifically looked at, Dr Heitmiller.

Primary Surgical Closure of Large Ventricular Septal Defects in Small Infants

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Herein, a policy of primary surgical closure of large ventricular septal defects in infants is reviewed. Forty-eight infants met criteria for inclusion in the study, and were divided into two groups based on weight: group 1 infants weighed 4 kg or less (n = 23), and group 2 infants weighed more than 4 kg (n = 25). Both groups had similar variation in ventricular septal defect location (paramembranous versus muscular) and number (single versus multiple), as well as incidence of major associated extracardiac diseases. No early deaths occurred in group 1, compared with 1 infant (4%) in group 2. Major complications occurred similarly in both groups (9% versus 12%). There were two late deaths in group 1 (9%) and none in group 2. No surviving patients have required a second ventricular septal defect operation, and the majority no longer receive anticongestive therapies. These results indicate that primary surgical closure of large ventricular septal defects, even multiple muscular defects, can be performed in very small infants with no difference in mortality or serious complication rates compared with larger infants. Protracted medical efforts to achieve larger size before primary repair and palliative pulmonary artery banding are not necessary.

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Infants with large ventricular septal defects (VSDs) and intractable congestive heart failure (CHF), growth retardation, and, less often, elevated pulmonary vascular resistance (PVR) constitute a substantial percentage of patient referrals to pediatric cardiothoracic surgeons. Although the majority tolerate primary surgical VSD closure with low morbidity and mortality, experience with younger and smaller infants has been variably less satisfactory. Most case series of infants undergoing primary VSD repair have reported perioperative mortality rates between 2% and 17%; however, mortality rates for infants less than 4 months of age or less than 4 kg in weight were much higher, between 9% and 75% [1–8]. Consequently, some authors have advocated protracted medical support until the infant with a large VSD is older and larger [3, 5], or pulmonary artery (PA) banding for very small infants [8, 9] or those with multiple muscular VSDs [7, 8, 10, 11] who require urgent surgical intervention.

We report the results of a policy of primary surgical closure of VSDs applied over the past 5 years to all symptomatic infants regardless of patient weight, location or number of VSD(s), or presence of associated major extracardiac diseases. Comparisons of preoperative, operative, and outcome variables were made between infants weighing 4 kg or less and those weighing more than 4 kg at the time of operation.

Material and Methods

The hospital records of infants (less than 12 months of age) who underwent surgical VSD closure at St. Louis (MO) Children's Hospital between March 1986 and May 1991 were reviewed. During this period, 47 infants underwent primary surgical closure of either a single large paramembranous VSD or multiple muscular defects. Infants who had undergone a prior operation to correct coarctation of the aorta or patent ductus arteriosus were included in the retrospective analysis. One additional infant underwent closure of multiple muscular VSDs after inadequate relief of symptoms after PA banding. Infants with tetralogy of Fallot, VSD associated with pulmonic valve stenosis or obstructing infundibular muscle bundles, and complex cardiac malformations were excluded from this study. The latter exclusion was waived for 3 infants with a form of double-outlet right ventricle with side-by-side great vessels, subaortic VSD, and no obstruction to pulmonary blood flow, because the clinical presentations and surgical procedures were comparable with those of infants with single large paramembranous defects.

The cohort ranged in age from 1 to 10 months, and for comparative purposes was divided based on weight at the time of operation into two groups: those less than or equal to 4 kg (group 1, n = 23) and those greater than 4 kg (group 2, n = 25). Reasons for referral included intractable CHF, growth retardation, elevated PVR, and inadequate palliation from PA banding. Infants with severe CHF and growth retardation all lacked sufficient clinical improvement despite treatment with digoxin, diuretics, and provision of increased dietary caloric intake. All but 3 patients

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underwent preoperative cardiac catheterization and angiocardiography. For the purpose of this study, VSDs were categorized as either (1) a single defect located in the paramembranous septum (including extension to the inlet, trabecular, or outlet regions) or (2) single or multiple defects in the muscular septum.

The surgical technique for VSD closure did not vary substantially during the study interval. A median sternotomy was used in all patients. Deep hypothermic circulatory arrest (nasopharyngeal temperature, 18°C), or cardiopulmonary bypass under moderate systemic hypothermia (28° to 30°C) with multidose cold asanguineous cardioplegic protection were the two operative strategies employed. A right atriotomy was performed in all patients, and in most, the VSD could be closed through this approach. Detachment of the septal leaflet of the tricuspid valve from the annulus was required to obtain adequate exposure in only a few infants. An additional right ventriculotomy was performed in 6 patients, and a left ventriculotomy was required in 1 (a patient in group 1 with dextrocardia and multiple muscular defects).

Ventricular septal defect closure was usually accomplished using a velour Dacron patch secured with interrupted pledgeted sutures. Bovine pericardial patch material was employed in a few of the smaller infants early in the study period. Some muscular defects could be closed primarily. The atrial septum was examined for defects in all patients, and if found, these were closed. A patent ductus arteriosus, if present, was ligated at the time of VSD repair.

Postoperative care did not change substantially during the interval studied. All infants had a postoperative echocardiogram before discharge to identify the presence and magnitude of any residual VSD. Follow-up information was abstracted from records kept by the patient's pediatric cardiologist.

Tests of statistical significance for numeric data included Student's *t* test, the Wilcoxon rank-sum test, and the Robust analysis of medians. For nominal data, either χ^2 analysis or Fisher's exact test was employed. Statistical significance was defined as a probability of rejecting the null hypothesis less than 5% (p value less than 0.05). For mortality rates, 95% confidence intervals (CIs) were calculated.

Results

The patients in group 1 ranged in weight from 2.2 kg to 4.0 kg, whereas those in group 2 were between 4.1 kg and 8.7 kg. With the exception of 1 infant in group 2, all patients had medically intractable CHF. More than half of the infants had major associated extracardiac diagnoses, with no significant difference between groups in this regard. These diagnoses included trisomy 21, the VACTERL association of congenital defects, cleft palate, bronchopulmonary dysplasia, chondrodysplasia, Klippel-Feil syndrome plus omphalocele, polysplenia syndrome, sepsis, pneumonia, and profound developmental delay plus seizure disorder in the context of a deletion in chromosome 1. At the time of repair, 3 infants (all in group 1) were dependent on assisted ventilation. Some patients in each group had previously undergone operations to correct accompanying cardiovascular abnormalities such as coarctation of the aorta, patent ductus arteriosus, and pulmonary sequestration. Still other patients had additional unrepaired cardiac abnormalities, including secundum atrial septal defect, patent ductus arteriosus, persistence of a left superior vena cava, and dextrocardia (Table 1).

Table 1. Preoperative Characteristics of the Patient Groups

Variable	Group 1	Group 2	*p* Value
Mean age ± SD (mo)	3.17 ± 1.34	6.12 ± 2.24	<0.01
Mean weight ± SD (kg)	3.18 ± 0.54	5.68 ± 1.23	<0.01
CHF	23/23 (100%)	24/25 (96%)	NS
Major extracardiac disease	12/23 (52%)	15/25 (60%)	NS
Prior cardiac operation	5/23 (22%)	2/25 (8%)	NS
Associated cardiac defect	7/23 (30%)	6/25 (24%)	NS
Mean RV/LV ± SD	0.90 ± 0.16	0.85 ± 0.20	NS
Mean Qp/Qs ± SD	3.71 ± 1.34	3.10 ± 1.17	NS
Mean PVR/SVR ± SD	0.18 ± 0.09	0.24 ± 0.14	NS
Paramembranous VSD	18/23 (78%)	24/25 (96%)	NS
Muscular/multiple VSD(s)	5/23 (22%)	1/25 (4%)	NS

CHF = congestive heart failure; NS = not significant; PVR/SVR = ratio of pulmonary to systemic vascular resistance; Qp/Qs = ratio of pulmonary to systemic blood flows; RV/LV = ratio of right ventricular to left ventricular systolic pressures; SD = standard deviation; VSD = ventricular septal defect.

Although no significant difference in PVR to systemic vascular resistance ratio was identified, group 2 did show a trend toward higher PVR. In addition, all infants who were referred for VSD repair because of concerns of increased PVR were in this group. Other hemodynamic variables measured during cardiac catheterization were similar between groups. Muscular/multiple VSDs were present in a higher percentage of group 1 infants, although the difference was not significant (see Table 1).

The only significant difference in operative technique between the groups was in frequency with which deep hypothermia and circulatory arrest were employed, being used more frequently in the smaller infants to provide improved visualization. The single major intraoperative complication in a group 1 infant was complete atrioventricular block requiring epicardial pacing to successfully discontinue cardiopulmonary bypass. This infant had a malalignment-type paramembranous VSD, and recovered normal atrioventricular conduction shortly after operation. In group 2, the only major intraoperative complication occurred in an infant with a paramembranous-outlet defect, in whom cardiopulmonary bypass was resumed three times before being successfully discontinued (Table 2).

Outcome data are summarized in Table 3. Overall mortality (early and late) was 6% (CI, 1.3% to 17.2%) for the entire cohort. No early deaths (before discharge from the hospital) occurred in group 1, compared with one death in group 2. The early mortality rates are therefore

Table 2. Operative Data

Variable	Group 1	Group 2	*p* Value
Circulatory arrest	15/23 (65%)	6/25 (24%)	<0.01
Ventriculotomy	4/23 (17%)	2/25 (8%)	NS
Intraoperative complication	1/23 (4%)	1/25 (4%)	NS
Mean CPB ± SD (min)	63.8 ± 21.7	56.1 ± 15.0	NS
Mean ACC ± SD (min)	31.7 ± 9.1	32.6 ± 10.6	NS
Mean arrest ± SD (min)	31.3 ± 7.7	32.5 ± 5.8	NS

ACC = aortic cross-clamp; CPB = cardiopulmonary bypass; NS = not significant; SD = standard deviation.

0% (CI, 0% to 15.4%) for group 1, 4% (CI, 0.1% to 20.3%) for group 2, and 2% (CI, 0.1% to 6.0%) for the entire series. The infant who died weighed 6.2 kg, had a deletion from chromosome 1, and had a single paramembranous VSD with elevated PVR (PVR/systemic vascular resistance ratio = 0.6). No intraoperative complications occurred. Postoperatively, the infant had development of low cardiac output, intermittent atrioventricular conduction block, and several episodes of pulmonary hypertensive crises with cardiac arrest before dying on postoperative day 4. No postmortem examination was performed.

Major nonfatal postoperative complications included perforation of the colon in a 2.2-kg infant, sepsis in a 3.7-kg infant, transient left phrenic nerve palsy in a 4.6-kg infant, and pulmonary hypertensive crises with cardiac arrest in a 4.7-kg infant. In contrast, minor complications were more frequent, including accelerated junctional tachycardia, mild CHF, hypertension, transient seizures, atelectasis/pneumonia, stridor, and superficial sternal wound infection. Such minor complications were more commonly seen in group 1 infants.

The distributions in number of postoperative days until assisted ventilation was discontinued and the number of days until discharge from the hospital were skewed. Hence, medians (rather than means) and the Robust analysis (rather than the classic *t* test) were used in the statistical analysis of these data. Group 1 infants required longer periods of assisted ventilation and convalescence in the hospital than did those in group 2.

The duration of follow-up ranged from 4 to 66 months with no significant difference between groups. In the entire cohort, 20/48 (41%) of the infants had small VSD patch leaks detected by echocardiogram before hospital discharge. Other authors have reported a similar residual VSD detection rate with early postoperative echocardiographic examination [12]. No patient required a second operation, and only 5 infants (10%) had murmurs or echocardiographic evidence of residual VSD at the most recent follow-up evaluation. The only infants in either group still maintained on anticongestive medications (digoxin or diuretics or both) were within 7 months of operation, and no cases of persistent growth retardation due to residual cardiac disease have been documented.

Table 3. Outcome Data

Variable	Group 1	Group 2	*p* Value
Early death	0/23 (0%)	1/25 (4%)	NS
Major complication	2/23 (9%)	3/25 (12%)	NS
Minor complication	10/23 (43%)	4/25 (16%)	<0.05
Median ventilator days (range)	3 (1–28)	1 (1–9)	<0.01
Median days to discharge (range)	13 (4–64)	6 (4–10)	<0.05
Mean F/U ± SD (mo)	24.4 ± 19.6	31.0 ± 20.8	NS
Late death	2/23 (9%)	0/24 (0%)	NS

F/U = follow-up; NS = not significant; SD = standard deviation.

There have been two late deaths, both in group 1. Thus, the late mortality rates were 9% (CI, 1.1% to 29.2%) and 0% (CI, 0% to 14.2%) for groups 1 and 2, respectively. Seven months after operation, an infant with dextrocardia and multiple VSDs who required a left ventriculotomy for repair died shortly after admittance to an outside hospital for respiratory failure due to respiratory syncytial virus pneumonia. No postmortem examination was performed. The other late death occurred in an infant with trisomy 21 who acquired *Klebsiella pneumoniae* sepsis 4 months after operation. A postmortem examination found the VSD patch intact, and no evidence of endocarditis was noted.

Comment

Among congenital heart defects, VSD is the most common [13, 14]. Its occurrence in isolation or in combination with other structural cardiac abnormalities frequently leads to symptoms of CHF such as tachypnea, feeding difficulties, and slow growth, and can complicate recovery from lower respiratory infections. Very small infants and those with major extracardiac diseases seem especially prone to development of severe CHF if the magnitude of left-to-right pulmonary recirculation is large. Furthermore, in this subset of infants, present outpatient anticongestive therapies often fail to ameliorate symptoms, leading those who care for such infants to recommend hospitalization for intensive supportive care, palliative operation such as PA banding, or early primary VSD repair.

Over the past 2 decades, most pediatric cardiothoracic surgical services have adopted a policy of primary surgical VSD closure when confronted with severely symptomatic infants. Early postoperative mortality rates have been generally around 5% [1–8], much lower than the 7% to 53% range observed for a two-stage approach of PA banding followed by later VSD repair and debanding [15–17]. Primary VSD repair has also led to a reduction in the incidence of serious PA band–related complications, and has more consistently improved long-term hemodynamic outcomes and "catch-up" growth rates [6, 8, 18, 19].

Very small infants with large paramembranous VSDs, infants with multiple muscular defects, or those who are severely debilitated remain a therapeutic challenge. For this subset of infants, mortality rates after primary VSD repair have been between 9% and 75% [1–8]. Collective analysis of the results from individual studies on all infants less than 4 months old, for example, yields an early (hospital) mortality rate of 24% [1–8]. Therefore, the risk of primary repair in these young infants (analogous to group 1 in the present study) has been equal to, or in excess of, that observed after a two-stage approach. The increased risk has been attributed to a higher prevalence of serious preoperative disability (mainly respiratory insufficiency), choice of standard cardiopulmonary bypass rather than circulatory arrest, overlooked or serious residual VSD resulting in persistent CHF after operation, management errors, and presence of associated lesions such as patent ductus arteriosus or coarctation [1–6].

Not infrequently there has been reluctance on the part of pediatric practitioners to subject very small and often very ill infant to the expected high risks associated with primary VSD closure. Instead, protracted efforts to improve growth using multiple anticongestive medications, high-calorie infant formulas, nasogastric tube feedings, and sometimes hospitalization are pursued, often at great financial and emotional cost to the patient's family. When these efforts fail, and urgent surgical intervention is deemed necessary, PA banding has been viewed as the lower risk procedure when compared with primary repair [7–11].

Past experience with PA banding at this institution parallels that reported in the literature regarding difficulty in obtaining a consistent degree of reduction in the pulmonary blood flow and regarding incidence of other complications (eg, band migration causing either uneven flows to each lung or pulmonic valve damage, and false aneurysm formation at the band site) [2, 10, 11]. For these reasons, primary VSD closure was adopted in 1986 as the preferred surgical management for all infants with VSD at our institution.

The results of this retrospective study indicate that satisfactory results can be obtained after primary surgical closure of large or multiple VSDs in infants weighing less than 4 kg. No significant differences in early, late, or overall mortality rates were apparent between groups 1 and 2. The smaller infants suffered a comparably low incidence of major complications as compared with their larger counterparts. Notably, none of the smaller infants died as a result of VSD operation. Even with a broad confidence interval (0% to 15.4%), the mortality for group 1 falls well below that observed for similar infants in a number of previous reports [1–8].

It should be emphasized that more than 50% of infants in this study had other serious extracardiac diseases, and many of the smaller infants were seriously ill enough to require intensive preoperative supportive care. The latter observation, coupled with the higher rate of minor postoperative complications, is likely inextricably linked to the longer periods of assisted ventilation and hospital-based convalescence required by the smaller infants. One could speculate, however, that the longer time and associated expense of hospitalization for these infants would be less than that expected from a two-stage surgical approach.

An intriguing aspect of our results is the outcome after primary repair of multiple muscular defects. Despite a small sample size (6 infants, 5 less than 4 kg), no serious perioperative complications were noted in these infants, all of whom required ventriculotomies. In the single instance where PA banding preceded VSD repair, that operation did not improve the patient's condition, and the infant remained dependent on assisted ventilation until VSD closure was accomplished. More experience with primary repair in patients with multiple muscular defects will clarify the prudence of this approach.

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of circulatory arrest, and perfusion variables during cardiopulmonary bypass did not correlate with mortality.

Permanent neurologic morbidity occurred in 9 patients, or 15% (9/60) of the series (Table 3). Focal cerebral infarction occurred in 7 patients, whereas diffuse ischemic injury occurred in 2. In 1 patient undergoing coronary artery bypass, the postoperative infarction was probably embolic in origin, as there was atherosclerotic debris noted in the aorta intraoperatively. Transient cortical blindness was recognized late in another patient; its relationship to HCA was uncertain. Five patients were mildly confused in the immediate postoperative period, but all improved by the time of discharge. One patient complained of transient blurred vision.

The only correlate of serious neurologic morbidity was intraoperative hypotension ($p < 0.05$). Type of operation, age, sex, emergency status, duration of circulatory arrest, and CPB perfusion variables did not correlate with neurologic morbidity. There were 12 late deaths. Nine (75%) were due to metastatic disease in patients who underwent nephrectomy for renal cell carcinoma. These nine deaths occurred between 2 and 39 months after operation. One patient with a thoracic aortic aneurysm died of ovarian carcinoma 13 months after aneurysm resection.

Actuarial survival of all HCA patients was 60% at 1 year and 37% at 3 years. For patients who had operation on the heart and great vessels, 1- and 3-year survival was 75.9% and 70%, respectively. After nephrectomy or adrenalectomy, 1- and 3-year survival was 75% and 23.4%.

Comment

Hypothermic circulatory arrest was used originally in the repair of congenital cardiac anomalies [14]. With experience and improvements in technique, operative mortality associated with HCA has been significantly reduced and the incidence of neurologic sequelae is low [15]. In 1960, Woodhall and associates [16] successfully employed HCA for craniotomy and resection of aneurysms. In 1963, Lillehei and co-workers [17] used HCA to treat a ruptured mycotic aortic aneurysm. These were important milestones and ushered in broader applications of HCA in adult surgery. Since then, the technique has been adopted for a wide variety of surgical procedures and is being used with increasing frequency. Its major value has been in prevention of life-threatening hemorrhage and in facilitating surgical approach to otherwise inaccessible structures, such as the aortic arch. However, a review providing perspective on its role in adult cardiac surgery has been lacking, and more importantly, knowledge of its limitations and dangers has been incomplete.

The central nervous system is the most sensitive organ to circulatory arrest. At normothermia, the central nervous system tolerates only 5 to 6 minutes of ischemia before irreversible injury occurs. However, hypothermia reduces cerebral metabolism and extends the central nervous system tolerance of ischemia, such that 45 to 60 minutes of "safe" ischemia is possible at 18° to 20°C. In this study, no consistent method was used to monitor cerebral activity. Crawford has suggested that electroencephalographic monitoring during the induction of hypothermia to assure electrical silence may correlate with better neurologic outcome. However, this has not yet been proved.

The cooling of blood and tissues may itself introduce complications. Rapid temperature change in blood can lead to formation of gaseous microemboli with the potential to compromise the cerebral circulation [18]. Furthermore, rapid cooling produces vasoconstriction, which may impede tissue perfusion and impair further cooling. This can lead to uneven cooling throughout the body. This phenomenon also raises the issue of which temperature, ie, nasopharyngeal, tympanic, rectal, blood, or bladder, is the most appropriate to monitor.

Hypothermia may also have deleterious effects on blood elements [19]. Consumption of several coagulation factors can lead to clinically significant coagulopathy and necessitate use of blood products. However, in this 5-year series, bleeding complications due to coagulopathy occurred in only 2 patients and were easily corrected.

The results of this study emphasize the importance of maintaining deep hypothermia during circulatory arrest. The finding that lowest rectal temperature, but not nasopharyngeal temperature, correlated with mortality may indicate that rectal temperature is a safer index of adequacy of cooling.

Neurologic morbidity was 15%. In several cases, it was unclear whether cerebral infarction occurred as a result of circulatory arrest, CPB, or the primary disease. Three patients with intraoperative stroke had postoperative hypotension due to poor cardiac function, which many have contributed to cerebral ischemia. One patient with cerebral emboli had atherosclerotic debris in the aorta. In another patient, postoperative cortical blindness was noted 1 week after HCA, but a second intervening operation obscured the possibility that HCA caused the cortical infarction.

Reported mortality after HCA varies considerably. Differences may be due to the diseases treated and the operative procedures employed. This study is unusual in examining the outcome of *all* adult surgical procedures using HCA over a 5-year period at a single institution. Mortality was 15% and correlated with higher rectal temperatures at the end of HCA, intraoperative hypotension, and longer periods of cardiopulmonary bypass.

In adults, HCA has been used most extensively in thoracic aortic surgery. This series demonstrates the applicability of HCA to coronary artery bypass grafting, to cardiovascular trauma, and to resection of unusual soft tissue tumors. The similar mortality rate for operations on the heart and great vessels compared with operations for intraabdominal malignancy support the role of HCA as a valuable adjunct in the management of selected complex surgical problems.

In summary, HCA is a facilitative technique that has enlarged the scope of operable lesions by reducing risk of hemorrhage. It enables the surgeon to work with precision in a relatively bloodless field. Although it is used mainly in children in the repair of congenital heart defects, the technique is being employed increasingly in adults with satisfying results. The safety of HCA is improved by maintaining deep hypothermia, by minimizing duration of extracorporeal circulation, and by maintaining stable perioperative hemodynamics.

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DISCUSSION

DR LARS G. SVENSSON (Houston, TX): I think this is a fine study, Dr Cameron. You looked at a lot of factors. We have recently analyzed our data. Six months ago we looked at 610 patients who underwent specifically aortic arch repairs and acute dissection repair. The incidence of global or hemispheric stroke was 7% with a 90% survival rate. We looked with logistic regression analysis at the predictors of stroke according to the circulatory arrest time. In the patients with less than 50 minutes of circulatory arrest no strokes occurred; at 15 minutes it increased to 5%; 45 minutes, 10%; and 90 minutes, 20%. On multivariate analysis we found the predictors to be age and circulatory arrest time, and another important predictor was the history of a previous stroke. Histology was also important, indicating to us that if there is atherosclerotic material in the arch at the time of repair this is a risk for embolization. As you mentioned, we also found the most important predictor for mortality was the total cardiopulmonary bypass time. In reference to that I was wondering if you included the circulatory arrest time in your calculation of total cardiopulmonary bypass time. That might have obscured your effect of circulatory arrest time. We also had several other predictors.

As far as your technique and the electroencephalography you mentioned, as I understood it, you arrested at a mean temperature of 20°C. We have found that the electroencephalogram does not become silent often at that temperature, particularly when you are looking at rectal temperature. Our impression is that often the rectal temperature falls quicker than the other temperatures, and this may be because you are cooling through the femoral artery and therefore perfuse the vessels supplying the rectum quicker and cooling them more rapidly. Could you comment on that?

We used to use steroids, 2 g of methylprednisolone, and we looked retrospectively at our patients and found the incidence of sepsis and multiple-organ failure was considerably higher in the patients so treated. We therefore have actually abandoned using steroids, with improvement, we believe, in the incidence of multiple organ failure. I was wondering if you use any other adjuncts, particularly if you are not cooling the patient until electroencephalographic silence occurs.

I had one other question, and that was whether you had looked at any of the psychiatric variables in these patients postoperatively. Obviously stroke is a fairly gross assessment of function after deep hypothermia and circulatory arrest, and perhaps psychiatric and neurophysiological tests might reveal other problems in these patients.

DR RONALD C. ELKINS (Oklahoma City, OK): I enjoyed your presentation very much. I likewise was concerned about your decision to use 20°C as a temperature for institution of hypothermic circulatory arrest. I personally have used 15°C based on the experience in Houston and others, which have demonstrated that the electroencephalogram does not become silent until one gets substantially below 20°C.

The second point is I think that there are abundant data that suggest that prolonged circulatory arrest, ie, greater than 45 minutes, is associated with a marked increase in cerebral dysfunction postoperatively. Have you attempted to develop any techniques that would allow you to have periods of reperfusion of the brain and recooling so that you could have an additional period of safety for conduct of your operation?

DR CAMERON: I thank Dr Svensson and Dr Elkins for their kind comments and constructive criticisms. I will try to answer each of the questions they have raised.

Dr Svensson first asked if we included the circulatory arrest time in our determination of the total cardiopulmonary bypass time. We did not, so I do not believe we obscured a possible relationship between circulatory arrest duration and mortality. I believe that the reason we did not see a relationship between stroke and duration of circulatory arrest is that most of our circulatory arrest times were less than 30 minutes.

Dr Svensson also asked about use of electroencephalography, and I would say that we are indebted to Drs Svensson, Coselli, and Crawford for pointing out the importance of electroencephalographic monitoring in circulatory arrest, something we will begin to use in our practice. We are impressed that the "20° rule" does not apply to all patients and that it is important to document cerebral silence by electroencephalography before stopping cooling.

Dr Svensson also asked about use of steroids. I must say this is a traditional practice that is unsubstantiated. If one were to poll our surgical group at Hopkins, most would say steroids are probably not having much effect, but conversely a single dose before induction of circulatory arrest is probably not contributing significantly to postoperative morbidity.

As pertains to assessment of psychiatric dysfunction after circulatory arrest, this was a retrospective review and we were not able to focus on that, but I would agree it would be a very interesting subject. Dr Timothy Gardner at our institution is prospectively studying many of these variables in patients undergoing coronary artery operations. Certainly the circulatory arrest group would be a particularly interesting one to study.

Dr Elkins raised the very important point that we do not know the optimal temperature for cerebral protection in circulatory arrest. This study has suggested to us that lower temperatures may be safer and that the extra time on bypass to achieve deeper hypothermia is probably a small price to pay to achieve better cerebral protection.

With regard to use of intermittent reperfusion to extend the period of safe circulatory arrest, we have no clinical experience with the practice, but it is something we are addressing in the laboratory. We are also pursuing pharmacologic means to improve the safety of circulatory arrest.

Chest Wall Stabilization With Synthetic Reabsorbable Material

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Experimental results and preliminary clinical experience with synthetic reabsorbable materials in chest wall reconstruction are reported. Six beagle dogs underwent chest wall resection involving three or four consecutive ribs. Reparative procedure was performed by construction of a polydioxanone-band grid, anchored to the adjacent undamaged ribs. A mild wound infection developed in 1 animal but resolved without rejection of the prosthesis. The experimental material has shown favorable properties, both mechanical and biological. Subsequently, 11 patients, with different indications, underwent reconstructive procedures of the chest wall with reabsorbable prostheses. No complications have occurred. Long-term stability was excellent in all patients, with a mean follow-up longer than 6 months. The advantages of reabsorbable compounds are pointed out along with the possible applications for chest wall reconstruction after chest wall resection.

(Ann Thorac Surg 1992;53:408–11)

A large number of tumors, both primary and secondary, may involve the thoracic wall, challenging the surgeon's ingenuity in devising complex reconstructive procedures. It is widely accepted that an aggressive resection is the key to successful treatment of all chest wall neoplasms [1–3]. On the other hand, not all thoracic defects require complex reconstructive procedures.

Surgical technique depends on several factors, among which the size and site of the defect seem to be most important. The problem posed by extensive full-thickness chest wall resection may be solved in different ways according to the surgeon's experience.

The goals of the various procedures applied are restoration of adequate ventilatory dynamics and protection of intrathoracic organs. Such objectives can be accomplished both with the use of prosthetic material and with muscle flaps. The latter require, generally, cooperation between plastic and thoracic surgical teams.

In recent years synthetic nonabsorbable prostheses have earned praise for providing better stability with shorter and simpler procedures. However, some complications have been reported, related to the properties of the employed material. Occasional reports have appeared in the recent literature concerning the use of absorbable compounds in chest wall reconstruction with favorable results [4].

This article reports an experiment on chest wall stabilization with synthetic absorbable material along with the initial clinical experience derived.

Experimental Research

Material and Methods

Six female dogs, aged 12 to 24 months, were included in the study. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No 85-23, revised 1985).

The dogs were submitted to operation under general anesthesia with endotracheal intubation. Anesthesia was induced with sodium thiopental (0.04 mg/kg intravenously) and maintained with oxygen, nitrous oxide, and halothane (1.5% to 2.0%). As soon as the pleural cavity was entered, ventilation was maintained mechanically. The animals were placed in the lateral position, and the skin was prepared with a solution of povidone-iodine.

The first 3 dogs were submitted to chest wall resection involving three consecutive ribs; in the other 3, four consecutive ribs were resected. Identical surgical procedure was adopted in the two groups.

A thoracic incision was performed at the level of the fifth intercostal space. The latissimus dorsi as well as the serratus anterior muscles were prepared and divided. Furthermore, some costal insertions of the latter muscle were detached so that the rib cage was exposed from the second to the seventh rib. Chest wall resection was carried out, involving three or four consecutive ribs in the midportion, the interposed soft tissues, and the underlying parietal pleura (Fig 1).

For the reparative phase, bands of polydioxanone measuring 1.5 × 60 cm were employed (PDS band; Ethicon, Somerville, NJ). The thoracic defect was repaired using an intrapleural grid of such material, anchored to the superior and inferior uninvolved rib (Fig 2). A pleural drain was inserted and positioned at the apex of the chest. The muscular layers were sutured over the absorbable prosthesis. Before extubation the chest tube was connected to

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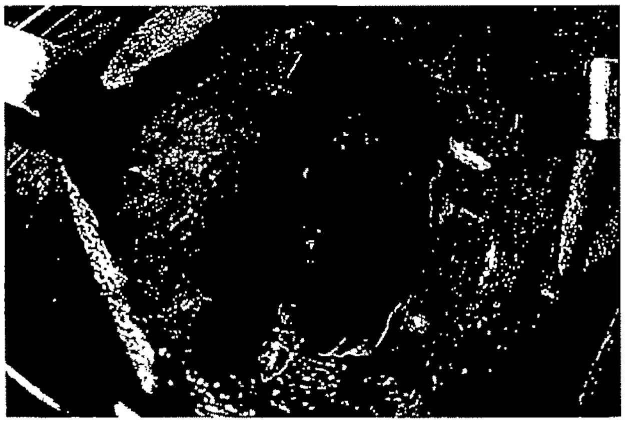

Fig 1. Experimental study: chest wall resection involving three consecutive ribs in the midportion and the interposed soft tissues.

a water seal apparatus and suction was added, in the range of 20 to 30 cm H_2O. Once a constant negative intrapleural pressure was achieved, the thoracic tube was removed and the animal extubated.

A prophylactic antibiotic regimen was started immediately postoperatively and maintained for 6 days.

Postoperative chest x-ray films were obtained at the 10th and 30th days.

Six months after operation all animals were sacrificed by intravenous administration of barbiturates and curariform drugs; pathological examinations of the chest wall and the underlying lung were then performed.

Results

Postoperative course was uneventful except for 1 animal in which a mild wound infection developed. With dressing and antibiotic therapy, this resolved without rejection of the prosthesis.

Excellent short-term and long-term stabilization was achieved in all cases.

In the majority of cases, postoperative radiological examination showed a mild pleural reaction beneath the reconstructed defect, without pleural effusion (Fig 3).

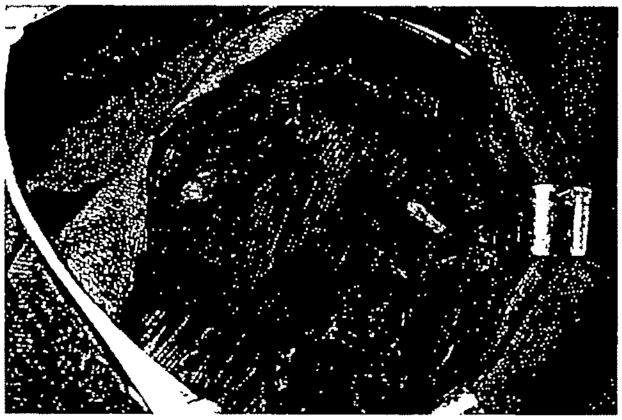

Fig 2. Experimental study: reparative procedure with a polydioxanone-band grid anchored to the superior and inferior uninvolved ribs.

Fig 3. Experimental study: x-ray film 30 days after the operation shows mild pleural reaction beneath the prosthesis; no pleural effusion is evident.

Pathological study of the chest wall and underlying lung showed complete absorption of the prosthesis and substitution by a thick scar, strongly adherent to the visceral pleura. Microscopic examination revealed this to be fibrous tissue with few inflammatory cells and without major foreign body changes.

Clinical Experience

Material and Methods

At the General Thoracic Surgery section of the Department of Surgery (R), University of Perugia Medical School, Italy, from 1986 to 1990, 11 consecutive patients were treated by full-thickness resection of the chest wall and immediate reconstruction with absorbable material. There were 6 men and 5 women. The age of the patients ranged from 40 to 77 years (mean age, 60 years). No patients received preoperative radiotherapy.

The procedures performed were as follows: en bloc pulmonary and chest wall resection, 7 patients; isolated chest wall resection, 2; right lower lobectomy with partial en bloc resection of the diaphragm, 1; and sternal resection, 1. Four consecutive ribs were resected in 1 patient; in the remaining 8, skeletal defects involved three consecu-

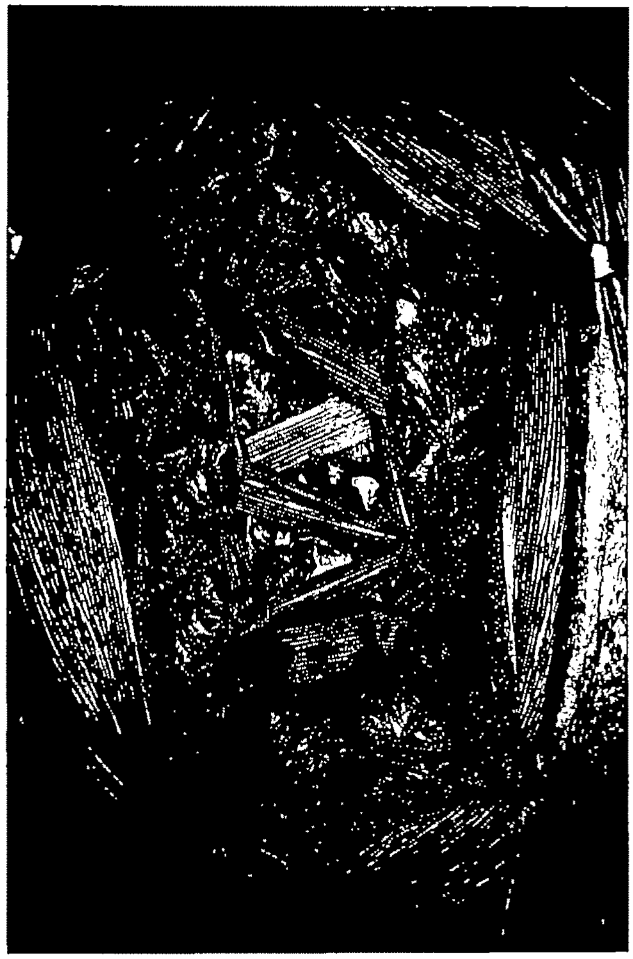

Fig 4. Clinical experience (sternal resection): polydioxanone-band grid anchored to the sternal and costal stumps; rectus abdominis muscles are retracted.

tive ribs. All resections included intercostal muscles and parietal pleura; in 1 patient, the overlying muscular layer was partially involved in the resection. One patient was submitted to resection of the lower two thirds of the sternum along with the fourth, fifth, and sixth costal cartilages.

Stabilization of the rib cage was achieved by a grid of polydioxanone bands anchored to the adjacent ribs, in the same fashion as in the experimental study. The diaphragmatic defect was repaired with polyglactin mesh (Vicryl, Ethicon) sutured with nonabsorbable stitches. The sternal defect was repaired with a polydioxanone-band grid placed as support for an overlying polyglactin mesh prosthesis (Figs 4, 5).

Tumor pathology was non–small cell bronchogenic carcinoma in 6 patients, primary chest wall tumor in 3, and metastatic involvement of the thoracic cage in 2.

Results

No perioperative deaths were observed. Postoperative course was uneventful in all patients except for the patient submitted to diaphragmatic reconstruction, in whom a transient pleural effusion developed. This resolved after chemical pleurodesis with tetracycline, keeping the chest tube in place for 11 days. Two patients had a slight degree of paradoxical motion of the chest wall, which eventually disappeared in the early postoperative period. The mean hospital stay was 11.7 days.

One patient died 4 months after operation of metastatic spread. All the remaining patients had a follow-up longer than 6 months (up to 30 months). The material was well tolerated in all patients: there were neither occurrence of late infections nor problems related to biological tolerance of the prostheses. Excellent long-term chest wall stabilization was achieved and cosmetic results were considered satisfactory in all cases.

Comment

At present, the optimal technique for chest wall reconstruction is far from being recognized. Myoplasties are theoretically preferable because they do not entail problems related to biological tolerance. On the other hand, some disadvantages do restrict the use of myoplasties: lengthy procedures, extensive surgical trauma, detach-

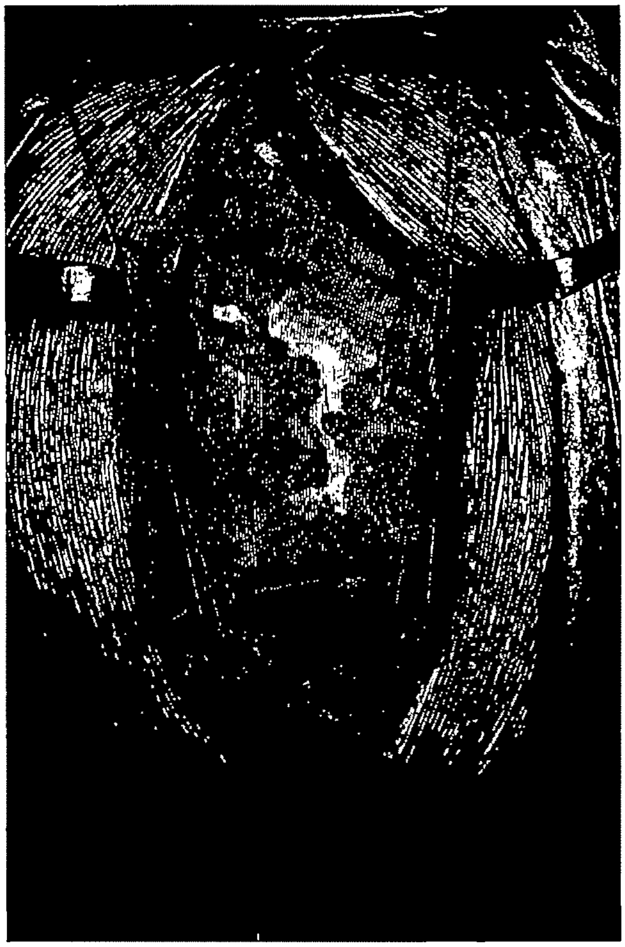

Fig 5. Clinical experience (sternal resection): polyglactin mesh placed over the reabsorbable grid.

ment of respiratory muscles, and sometimes inadequate stabilization.

In recent years the role of prosthetic materials in the repair of a thoracic defect has earned interest for providing better stability with shorter and simpler surgical procedures. Several nonreabsorbable prostheses have been used to stabilize defects of the thoracic cage, alone or in combination with muscular flaps. Different materials (polypropylene mesh [Marlex], polyethylene mesh [Prolene], methylmethacrylate, and, recently, polytetrafluoroethylene soft patches [Gore-Tex]) have proved to be suitable for chest wall stabilization, as previously reported [5].

However, the use of these materials is not totally free from complications, the most important being infection due to implantation in a contaminated field or to inadequate incorporation. According to Arnold and Pairolero [6], the majority of wound problems in such cases occur in a previously contaminated field. These authors report 3 of 49 patients who required removal of Prolene mesh because of subsequent wound infection [7]. Other authors, after a mean follow-up of 4.2 years, observed a partial infection of Marlex mesh in 25% of their patients [8]. The risk of late infection remains even several years after implantation, as reported by Eschapasse and Gaillard [9]. This seems to be more likely if postoperative radiotherapy is required. The surgeon must take into account this possibility especially in case of primary chest wall tumors.

A rigid plaque such as methylmethacrylate in combination with Marlex mesh is employed for the repair of very large defects to maintain the curved surface of the lateral chest wall. Methylmethacrylate seems to have several disadvantages: it is rigid, poorly incorporated, and difficult to fix, and it needs to be fashioned extracorporeally (owing to the risk of general toxicity if the resin is polymerized in situ) [10]. Furthermore, it is sometimes necessary to add steel mesh to prevent possible fragmentation of the plaque [11]. For these reasons methylmethacrylate should be used only when strictly necessary, an event that does not seem to occur very frequently.

The ideal prosthetic material for chest wall reconstruction should feature good tolerance, resistance to infection, radiolucency, and facility of modeling. It should offer solid protection to the intrathoracic organs, and it should be capable of providing mechanical support at least for the period required for the healing process to be completed.

According to our experience, synthetic absorbable materials are particularly suitable for chest wall reconstruction. Both polyglactin mesh and polydioxanone band are knitted materials, so fibroid tissue can easily grow through the prosthesis. After the absorption time is completed, the prosthesis is entirely substituted by a thick scar, sufficient to provide stability to the chest wall and protection to intrathoracic organs. On the other hand, even in reconstructions with nonreabsorbable mesh, long-term stability seems to be due to the host tissue. In fact, several authors report the lack of abnormal chest wall motion upon removal of such prostheses during a period ranging from 3 to 80 months after implantation [9, 12]. Thus once the healing process is completed, persistence of the mesh seems to be no longer an advantage because problems related to infection are always possible.

After extensive chest wall resections the simple technique of an absorbable grid allows restoration of a relatively curved chest wall surface, and it may represent a valid support for an overlying myoplasty.

Another favorable property of polydioxanone to be emphasized is its relative resistance to infection, which permits the use of this material even in mildly infected areas. Such material is characterized by a very long absorption time (roughly 180 days), which provides adequate stability to the repair until completion of the physiologic healing processes by the host. Complete absorption reduces functional sequelae and avoids, in the long term, any problem related to biological tolerance. The use of absorbable prostheses appears to be particularly indicated for the repair of chest wall defects in patients needing postoperative radiotherapy. After extensive chest wall resection a grid of absorbable material, as support of an overlying myoplasty, seems to represent a valid alternative to the use of a composite prosthesis with methylmethacrylate.

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Iron Chelation in Myocardial Preservation After Ischemia-Reperfusion Injury: The Importance of Pretreatment and Toxicity

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Oxygen-derived free radicals have been implicated in myocardial ischemia-reperfusion injury. It has been proposed that deferoxamine, an iron chelator, improves myocardial preservation by reducing the iron-catalyzed production of the hydroxyl radical. The objectives of this study were to define the appropriate timing of iron chelation therapy and the dose-response properties of deferoxamine. Isolated working rat hearts were subjected to 25 minutes of normothermic global ischemia. Deferoxamine was given as pretreatment (n = 39; doses of 10 or 30 mg/kg), added to cardioplegic solution (n = 43; doses 0.46 to 1.90 mmol/L), or administered upon reperfusion (n = 52; doses 0.15 to 0.76 mmol/L) and compared with saline controls (n = 25). Deferoxamine pretreatment improved survival at each dose from a control value of 44% to 71% and 72% ($p < 0.05$), respectively. A cardioplegia dose of 0.46 mmol/L improved survival from 48% to 75%. Higher doses reduced survival and implied a toxic effect. Reperfusion therapy did not alter survival. Regardless of time of administration, deferoxamine did not improve ventricular function or adenosine triphosphate levels. Deferoxamine given as pretreatment 1 hour before ischemia at doses of 30 mg/kg, and perhaps as low as 10 mg/kg, significantly improved survival. The addition of deferoxamine to cardioplegic solution was safe and may be protective at approximately 0.50 mmol/L; however, toxicity should be considered at concentrations greater than 0.76 mmol/L. These data support the postulate that iron catalysis is involved in the production of oxygen-derived free radicals during ischemia-reperfusion injury. We conclude that pretreatment before ischemia is an important component of iron chelation therapy in myocardial preservation.

(Ann Thorac Surg 1992;53:412–8)

Oxygen-derived free radicals have been implicated in myocardial ischemia-reperfusion injury [1, 2]. Recent investigations have demonstrated enhanced myocardial preservation by the use of oxygen free radical scavengers [3–6]. The Haber-Weiss and Fenton reactions produce the most toxic oxygen species, the hydroxyl radical ($^{\cdot}OH$), which has no known natural defenses to combat it. It is readily formed in biologic systems in the presence of transition metals, particularly iron. Iron catalyzes the two-step Fenton reaction, which has the faster rate constant at physiologic pH. Ferric iron (Fe^{3+}) is reduced to its ferrous state (Fe^{2+}) by interacting with the superoxide anion and then is reoxidized by hydrogen peroxide as summarized in the following reactions:

$$^{\cdot}O_2^- + Fe^{3+} \rightarrow O_2 + Fe^{2+}$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH + {}^{\cdot}OH$$

It has been proposed that chelation of ferric iron with deferoxamine reduces the production of the hydroxyl radical, thereby reducing myocardial ischemia-reperfusion injury [7–12]. Deferoxamine is an affective iron chelator with a low molecular weight (Desferal [CIBA-GEIGY, Summit, NJ]; deferoxamine mesylate, 656.79 daltons) capable of entering the intracellular space [13]. Evidence has accrued to support the potential role of iron chelation in myocardial protection [9–12, 14–20]. However, its precise importance has yet to be completely defined. The purpose of this study was to define the appropriate timing of iron chelation therapy with respect to ischemia and the dose-response relationships of deferoxamine for improved myocardial protection.

Material and Methods

Male Sprague-Dawley rats weighing 350 to 450 g were anesthetized with an intraperitoneal injection of 7.2% chloral hydrate (0.5 mL/100 g) and given 400 units of sodium heparin. The hearts were rapidly excised and immersed in modified Krebs-Henseleit solution [21] at 2°C and placed on a Langendorff [22] apparatus as modified by Neely and associates [23]. The aorta was cannulated and perfused in a retrograde manner with modified Krebs-Henseleit buffer solution at 37°C with a hydrostatic

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pressure of 90 cm of H_2O. The components of the Krebs-Henseleit buffer are as follows:

Na^+	142 mEq/L
K^+	5.8 mEq/L
Cl^-	122 mEq/L
HCO_3^-	25 mEq/L
Ca^{2+}	3.0 mEq/L
Mg^{2+}	2.4 mEq/L
SO_4^{2-}	2.4 mEq/L
$H_2PO_4^-$	1.2 mEq/L
pH	7.4–7.5
Oxygen tension	450–550 mm Hg
Carbon dioxide tension	30–35 mm Hg
Insulin	0.4 U/L
Glucose	15 mmol/L
Aspartic acid	1.86 mg/L
Asparagine	8.99 mg/L
Glutamic acid	17.65 mg/L
Glutamine	95.27 mg/L
Serine	25.96 mg/L
Threonine	24.17 mg/L
Glycine	25.24 mg/L
Alanine	29.05 mg/L
Methionine	8.05 mg/L
Valine	22.03 mg/L
Isoleucine	14.17 mg/L
Leucine	21.77 mg/L
Phenylalanine	11.40 mg/L
Tyrosine	12.50 mg/L
Lysine	69.43 mg/L
Arginine	20.73 mg/L
Proline	12.43 mg/L
Cysteine	7.88 mg/L
Tryptophan	10.21 mg/L
Histidine	44.97 mg/L

The pulmonary artery was incised to decompress the right ventricle. The hearts and perfusate were maintained at a temperature of 37°C using a water-jacketed glass apparatus. The perfusate was oxygenated with 95% oxygen and 5% carbon dioxide and filtered by a 0.2-μm Pall filter (Pall Biomedical Inc, Fajardo, PR) and was not recirculated. The left atrium of each heart was cannulated, and after 15 minutes of normothermic retrograde perfusion the hearts were placed in the working mode. The hydrostatic pressure of the perfusate into the left atrium was 15 cm H_2O. The left ventricle ejected into a compliance chamber with a 2.5-mL air cap against a hydrostatic pressure of 80 cm H_2O. While in the working mode the perfusate was recirculated through a 0.2-μm in-line Pall cardioplegia filter.

After 15 minutes in the working mode, hemodynamic measurements were recorded (Gould Brush 480; Gould Inc, Oxnard, CA). Aortic pressures and heart rates were measured by a pressure transducer (Gould Statham P23; Gould Inc) placed in-line with the aortic cannula. Aortic and coronary outputs were measured by timed volumetric collections of the aortic and right heart effluent, respectively. Three measurements were obtained at 5-minute intervals, the average of which was used to represent the preischemic state. Hearts with rates less than 200 beats/min, aortic flows less than 42 mL/min, or coronary flows greater than 60% of the aortic flow were excluded.

Cardiac arrest was accomplished with a single 20-mL dose of cardioplegic solution consisting of 15 mmol of KCl added to 1 L of oxygenated modified Krebs-Henseleit buffer. The cardioplegia was filtered through a 0.2-μm Pall filter and delivered at a hydrostatic pressure of 80 cm H_2O at 37°C. After 25 minutes of normothermic global ischemia the hearts were reperfused in a retrograde manner and, after 15 minutes of reperfusion, converted back to the working mode. Hemodynamic measurements were repeated at 5-minute intervals after 15 minutes of equilibration in the working mode. The average of three measurements represented the postischemic state. At the conclusion of these measurements each heart was freeze-clamped with Wollenberger tongs and stored in liquid nitrogen.

Three treatment groups were evaluated. Deferoxamine mesylate was either administered as pretreatment to the intact animal (n = 39), added to the cardioplegia (n = 43), or included in the reperfusate (n = 52). Pretreatment animals were given either 10 mg/kg (n = 14) or 30 mg/kg (n = 25) of deferoxamine intramuscularly in the right hindquarter 1 hour before excision of the heart. Controls (n = 25) were given an equal volume of normal saline solution. In the second experimental group, deferoxamine was added to the hyperkalemic oxygenated modified Krebs-Henseleit cardioplegic solution at concentrations of 0.46 mmol/L (n = 16), 1.14 mmol/L (n = 13), and 1.90 mmol/L (n = 14). These were compared with controls (n = 21) receiving standard hyperkalemic buffer cardioplegia. Finally, deferoxamine was added to the reperfusate in doses of 0.15 mmol/L (n = 17), 0.46 mmol/L (n = 21), and 0.76 mmol/L (n = 14) and compared with controls (n = 21). Doses were chosen to be comparable with previous studies cited in the literature. Concentrations were selected in an attempt to deliver similar total doses; however, in doing so, cardioplegia with "low-dose" deferoxamine was not specifically investigated. All solutions were prepared by the National Institutes of Health media service using commercial reagents. Although levels were not measured, 3 to 7 μmol/L of iron was considered to be present in the preparation as previously reported by other investigators [9].

All animals had free access to water and standard laboratory chow (Purina Rat Chow; Ralston Purina, St. Louis, MO) before the experiment and were treated humanely according to guidelines established by the National Institutes of Health ("Guide for the Care and Use of Laboratory Animals," NIH publication No. 85-23, revised 1985).

Heart rates and systolic, diastolic, and mean blood pressures were measured by transducer. Coronary and aortic flows were measured by timed volumetric collections, with the sum equal to cardiac output. Stroke volume was calculated by dividing the cardiac output by the heart rate. Survival was defined as the ability to produce a measurable aortic flow, specifically 4 mL/min or greater. Adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) analyses were performed using standard high-performance liquid chromatography techniques and measured in micromoles per gram of soluble protein. Extraction was performed at 0°C with 6% perchloric acid, and potassium hydroxide was used for neutralization. The high-performance liquid chromatography system included Gilson Medical Electronics Inc model 302 pumps, model 811 dynamic mixer, model 116 ultraviolet detector, and model 620 Data Master, and a Whatman Partisphere C-18 reversed-phase column to separate nucleotides.

Statistical analyses were performed by a personal computer (IBM PS2) using SAS statistical software (Statistical Analysis Systems Institute, Cary, NC). The appropriate Student's *t* test was used to compare preischemic and postischemic states, and survival was evaluated by χ^2 analysis. Statistical significance was defined as a *p* value less than 0.05. All values were expressed as the mean ± the standard error of the mean.

Results

Survival

Survival, as defined by the ability to produce a measurable aortic flow (4 mL/min or greater) after 25 minutes of global normothermic ischemia, improved when deferoxamine was administered before ischemia. Pretreatment provided the greatest protection (Fig 1A). Eleven of the 25 control animals (44%) survived ischemia compared with 10 of 14 (71%) for the 10 mg/kg pretreatment group (p = 0.09). Survival was 72% (18/25) when 30 mg/kg of deferoxamine was administered ($p < 0.05$). Deferoxamine added to the standard cardioplegic solution resulted in improved survival at the 0.46 mmol/L dose to 75% (12/16) when compared with the control value of 48% (10/21). This approached, but did not reach, statistical significance (p = 0.09). However, larger doses of 1.14 mmol/L and 1.90 mmol/L decreased survival to 38% and 29%, respectively (Fig 1B). Although a downward trend was apparent, this did not reach statistical significance. Reperfusion with perfusate containing deferoxamine did not influence survival at doses of 0.15 mmol/L or 0.46 mmol/L; the survival rates of 41% (7/17) and 43% (9/21) were similar to the control value of 48% (10/21). An increased dose of 0.76 mmol/L decreased survival to 29% (4/14) (p = not significant).

Myocardial Function

Myocardial functional recovery of hearts surviving ischemia and given deferoxamine pretreatment were compared with controls. Results of functional recovery are reproduced in Table 1. There was no appreciable difference found in heart rate or in systolic, diastolic, or mean blood pressures. Aortic flows were approximately 58 mL/min in all groups and decreased to about 32 mL/min or 60% of the preischemic values. Coronary flows decreased roughly 15%. Postischemic cardiac outputs were about two thirds of preischemic values, decreasing from approximately 76 to 50 mL/min in all groups. Average stroke volume before ischemia was 0.30 mL/beat in all groups and decreased to the 0.20 mL/beat level, a 30% decrease. No significant differences were found in any subset.

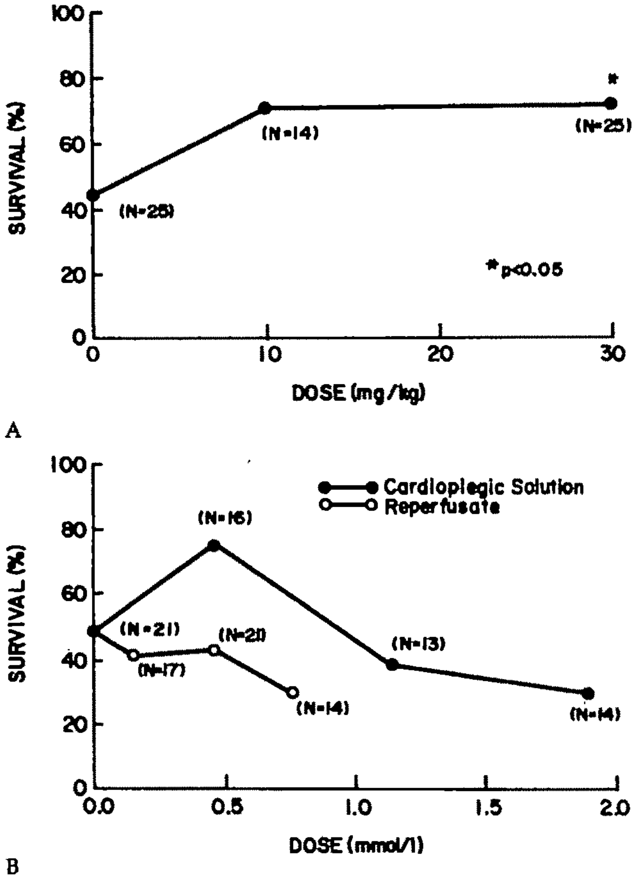

Fig 1. (A) Survival after 25 minutes of normothermic global ischemia in percent versus pretreatment dose of deferoxamine in milligrams per kilogram. (B) Survival after 25 minutes of normothermic global ischemia in percent versus cardioplegia and reperfusion treatment. Concentration of deferoxamine is expressed in millimoles per liter.

Functional recovery using cardioplegic solution enriched with deferoxamine was compared with controls receiving hyperkalemic Krebs-Henseleit buffer. Treated hearts did not have a statistically significant difference in heart rate or in systolic, diastolic, or mean blood pressure. Aortic flows were more heterogeneous, with preischemic values ranging from 58 ± 3 mL/min for controls to 74 ± 5 at 1.90 mmol/L. All postischemic values represented approximately a 50% recovery. However, at 1.14 mmol/L, aortic flow recovered only 25%, which approached, but did not reach, statistical significance (p = 0.06). This observation was also reflected in the cardiac output and stroke volume. Cardiac output recovered 41% compared with 60% for controls. Postischemic stroke volume was 0.13 (44%) versus a control value of 0.18 mL/beat (64%). On a percentage change basis, these observations approached statistical significance (p = 0.08 and 0.05, respectively). Cardiac output and stroke volume for the other doses were similar to controls.

Table 1. Hemodynamic Data for Control and Deferoxamine-Treated Animals Before and After 25 Minutes of Normothermic Ischemia[a]

Group	Heart Rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Mean BP (mm Hg)	Aortic Flow (mL/min)	Coronary Flow (mL/min)	Cardic Output (mL/min)	Stroke Volume (mL/beat)
Pretreatment With Deferoxamine								
Controls								
Pre	258.9 ± 10.0	101.6 ± 2.9	33.2 ± 2.6	63.8 ± 1.7	57.1 ± 2.7	19.6 ± 1.3	75.9 ± 3.2	0.29 ± 0.02
Post	243.1 ± 9.2	95.1 ± 2.7	41.8 ± 2.6	63.7 ± 1.8	33.2 ± 4.3	16.0 ± 1.4	49.2 ± 5.4	0.20 ± 0.02
10 mg/kg								
Pre	267.8 ± 10.3	100.1 ± 2.4	34.8 ± 3.3	62.3 ± 1.8	59.7 ± 3.5	20.1 ± 0.7	79.7 ± 3.6	0.30 ± 0.01
Post	237.8 ± 9.2	94.3 ± 2.3	43.7 ± 2.8	62.9 ± 1.4	30.0 ± 2.9	15.9 ± 1.0	45.9 ± 3.5	0.19 ± 0.01
30 mg/kg								
Pre	266.7 ± 8.4	100.6 ± 2.4	34.7 ± 1.4	64.2 ± 1.1	58.2 ± 2.7	20.6 ± 0.9	77.2 ± 3.2	0.30 ± 0.01
Post	248.7 ± 9.2	94.7 ± 2.9	43.2 ± 1.5	64.9 ± 1.2	34.6 ± 3.9	15.4 ± 1.1	49.9 ± 4.5	0.20 ± 0.02
Cardioplegic Solution With Deferoxamine								
Controls								
Pre	277.6 ± 12.2	97.3 ± 3.6	33.4 ± 2.3	62.2 ± 1.7	57.8 ± 3.3	21.0 ± 1.4	78.7 ± 4.1	0.29 ± 0.01
Post	261.6 ± 18.6	89.5 ± 3.4	42.3 ± 2.6	57.8 ± 3.3	29.5 ± 5.4	18.1 ± 2.4	47.3 ± 6.5	0.18 ± 0.02
0.46 mmol/L								
Pre	293.7 ± 12.5	95.5 ± 2.9	36.1 ± 1.9	62.8 ± 1.5	63.9 ± 3.1	24.2 ± 1.8	88.1 ± 4.0	0.31 ± 0.02
Post	244.1 ± 12.4	88.1 ± 2.6	42.3 ± 2.0	60.1 ± 1.2	28.9 ± 4.5	19.7 ± 1.9	48.6 ± 5.7	0.20 ± 0.02
1.14 mmol/L								
Pre	283.6 ± 19.7	96.5 ± 5.2	32.9 ± 3.8	61.6 ± 1.4	65.1 ± 2.5	24.5 ± 4.0	89.6 ± 6.2	0.32 ± 0.02
Post	264.0 ± 23.3	79.3 ± 2.7	49.1 ± 0.5	60.5 ± 0.8	16.3 ± 3.9	20.5 ± 3.6	36.8 ± 6.3	0.13 ± 0.02
1.90 mmol/L								
Pre	262.5 ± 21.3	114.0 ± 7.8[b]	25.2 ± 3.2	65.0 ± 2.4	74.2 ± 5.0	21.1 ± 1.3	95.3 ± 6.3	0.37 ± 0.02
Post	232.5 ± 25.9	98.7 ± 6.7	38.5 ± 3.4	63.0 ± 2.2	38.5 ± 8.7	15.5 ± 2.1	54.0 ± 9.0	0.23 ± 0.02
Reperfusion With Deferoxamine								
Controls								
Pre	277.6 ± 12.2	97.3 ± 3.6	33.4 ± 2.3	62.2 ± 1.7	57.8 ± 3.3	21.0 ± 1.4	78.7 ± 4.1	0.29 ± 0.01
Post	261.6 ± 18.6	89.5 ± 3.4	42.3 ± 2.6	57.8 ± 3.3	29.5 ± 5.4	18.1 ± 2.4	47.3 ± 6.5	0.18 ± 0.02
0.15 mmol/L								
Pre	281.1 ± 13.2	101.9 ± 3.0	32.7 ± 2.0	62.7 ± 1.3	61.9 ± 5.6	21.0 ± 0.8	82.9 ± 6.2	0.30 ± 0.02
Post	246.3 ± 6.3	95.2 ± 2.5	40.4 ± 2.5	61.2 ± 0.9	38.9 ± 6.2	16.2 ± 0.6	54.3 ± 6.6	0.23 ± 0.03
0.46 mmol/L								
Pre	272.0 ± 8.5	99.1 ± 2.3	31.2 ± 31.6	62.0 ± 1.1	64.0 ± 1.8	20.7 ± 0.9	84.7 ± 2.5	0.31 ± 0.01
Post	242.9 ± 7.3	84.8 ± 2.9	45.3 ± 0.9	59.6 ± 1.0	21.8 ± 3.8	17.7 ± 1.3	39.4 ± 4.3	0.16 ± 0.02
0.76 mmol/L								
Pre	287.7 ± 16.9	105.2 ± 5.6	32.9 ± 3.9	68.0 ± 2.2	64.6 ± 3.8	21.9 ± 1.5	86.3 ± 3.8	0.31 ± 0.03
Post	262.0 ± 6.5	96.7 ± 3.7	43.3 ± 2.1	66.3 ± 2.2	38.5 ± 3.2	22.0 ± 5.5	60.5 ± 4.1	0.23 ± 0.02

[a] All values are expressed as mean ± standard error of the mean. [b] $p < 0.05$.

BP = blood pressure.

Finally, deferoxamine added to the perfusate showed no appreciable change in heart rate or in systolic, diastolic, or mean blood pressure. Aortic flow recovery was approximately 60% with the 0.15 and 0.76 mmol/L concentrations compared with 50% for controls. This did not reach statistical significance. In fact, at the dose that improved survival, 0.46 mmol/L, aortic flow was actually lower at 34% of the preischemic value, which approached but did not reach statistical significance ($p = 0.10$). Similar trends were seen with cardiac output and stroke volume, with a greater recovery of cardiac output at the 0.15 and 0.76 mmol/L concentrations (65% and 71%) compared with controls (60%), and a decrease to 46% at 0.46 mmol/L. No statistically significant differences were found.

Adenosine Triphosphate Analysis

Results of ATP analysis are printed in Table 2. Adenosine triphosphate, ADP, and AMP levels did not differ with pretreatment. Levels of ADP and AMP were lower at the 0.46 mmol/L cardioplegic concentration, which coincided with improved survival. This was also true at the 1.14

Table 2. Nucleotide Levels as Determined by High-Performance Liquid Chromatography in Controls and Deferoxamine-Treated Animals After 25 Minutes of Global Normothermic Ischemia[a]

Group	AMP	ADP	ATP
Pretreatment			
Controls	0.45 ± 0.05	0.87 ± 0.07	1.59 ± 0.17
10 mg/kg	0.45 ± 0.05	0.82 ± 0.06	1.46 ± 0.11
30 mg/kg	0.53 ± 0.04	0.92 ± 0.04	1.54 ± 0.10
Cardioplegia			
Controls	0.43 ± 0.05	0.81 ± 0.06	1.48 ± 0.21
0.46 mmol/L	0.26 ± 0.03[b]	0.61 ± 0.04[b]	1.25 ± 0.11
1.14 mmol/L	0.19 ± 0.04[b]	0.41 ± 0.10[b]	1.43 ± 0.16
1.90 mmol/L	0.44 ± 0.08	0.86 ± 0.15	1.32 ± 0.11
Reperfusate			
Controls	0.43 ± 0.05	0.81 ± 0.06	1.48 ± 0.21
0.15 mmol/L	0.46 ± 0.05	0.78 ± 0.02	1.45 ± 0.08
0.46 mmol/L	0.46 ± 0.07	0.76 ± 0.07	1.22 ± 0.13
0.76 mmol/L	0.44 ± 0.04	0.84 ± 0.06	1.46 ± 0.11

[a] Values are expressed in micromoles per gram of soluble protein. [b] $p < 0.05$ versus control.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

mmol/L dose. Although ADP and AMP levels were lower, when viewed with respect to the lower initial ATP level, the proportion of nucleotides in the ATP moiety is about 55% of the total at each dose. Reperfusion with deferoxamine revealed no statistically significant change in ATP, ADP, or AMP levels compared with controls. No method of deferoxamine therapy improved preservation of stored ATP.

Comment

Recent investigations in myocardial ischemia-reperfusion injury have focused on the iron-catalyzed production of the hydroxyl radical. Iron is available from the intracellular low molecular weight pool, hemosiderin, ferritin, non-protein bound iron, and transferrin, and is released from granulocyte lactoferrin [7]. Deferoxamine binds ferric iron ($K_d = 10^{31}$) but has no affinity for the reduced ferrous ion. It can remove iron from ferritin, hemosiderin, and to a lesser extent transferrin (10% to 15%), but not from the porphyrin system, ie, hemoglobin [24]. Deferoxamine is a safe agent used in iron-overloaded patients with thalassemia up to doses of 50 mg/kg [8]. In vitro preparations have demonstrated the ability of deferoxamine to inhibit lipid peroxidation and limit the formation of hydroxyl radicals from superoxide species [25]. Other studies have also shown deferoxamine to be a superoxide scavenger at certain doses [26] but probably not at concentrations of less than 1 mmol/L [27]. These properties make deferoxamine a suitable candidate to be implemented in myocardial preservation investigations.

Previous reports using deferoxamine for myocardial preservation during ischemia-reperfusion injury have yielded conflicting results. This reflects the heterogeneity of the models used and the difficulty of comparing in vivo with ex vivo models, histochemical and ultrastructural analyses with those of ventricular function, global with regional models of ischemia, and administration of deferoxamine at different phases of ischemia. The objectives of the present study were to determine the optimal dose and timing of deferoxamine therapy. An ex vivo model was chosen to assure precise control of preload, afterload, circuit resistance, and temperature. The drawback of an ex vivo model was defining the endpoint of survival, a self-evident state in the intact animal. The ability to produce a forward aortic flow was chosen as the criterion in an attempt to produce clinically applicable data; a reported significant improvement in left ventricular (LV) mechanics may not accurately identify the heart capable of supporting the circulation. The choice of 4 mL/min was the lowest detectable in the preparation. This criterion only affected one heart in the pretreatment group and, in fact, only 10 hearts of all those included in the study had a postischemic aortic flow of 10 mL/min or lower. These were evenly distributed among the experimental groups.

The model had several additional characteristics. Normothermia was used to exclude the protective properties of hypothermia. This was a model of global ischemia designed to simulate cardiopulmonary bypass; an asanguineous perfusate was used to exclude the protective effects of blood and the superoxide scavengers and iron it transports. The model chosen was one of severe ischemia designed so that fewer than 50% of hearts survived ischemia and those that did had depressed LV function. Hence, any small improvement in either would be detectable. Results should be interpreted in this context, realizing that any reduction in myocardial injury with a model of normothermic global ischemia may not be totally applicable to the clinical setting of hypothermia used during cardiopulmonary bypass or regional ischemia present during acute myocardial infarction. Finally, ATP analysis was chosen as a marker of cellular biochemical function. Timing of deferoxamine therapy was designed to examine each phase of ischemia-reperfusion injury, namely before (pretreatment), during (cardioplegia), and after ischemia (reperfusion). Finally, most previous studies have used a single dose of deferoxamine. The present study tested both efficacy and toxicity by developing dose-response relationships for each phase of ischemia.

Ex vivo studies suggest that deferoxamine improves membrane stability after ischemia but does not improve LV function. Myers and co-authors [9] exposed rabbit hearts to 1 hour of normothermic global hypoxia. Deferoxamine (0.5 mmol/L) added to the perfusate decreased creatine kinase release after ischemia, and myocardial histology was better preserved. In a model of regional ischemia, Bernier and colleagues [14] noticed a significant reduction in arrhythmias and a prolongation of normal sinus rhythm during reperfusion when deferoxamine (150 μmol/L) was present in the perfusate. In vivo experiments reveal similar findings. Reddy and co-workers [15] subjected dogs to coronary artery occlusion. Animals receiving deferoxamine (10 mg/kg) before occlusion had a significant reduction in infarct size. There was no change in ventricular function or regional blood flow. In a similar model of regional ischemia, Bolli and associates [16] noted no changes in regional blood flow or hemodynamics. Similar results were reported in a rabbit model by Maxwell and colleagues [17]. The consensus of these investigations demonstrates a reduction in infarct size in a model of regional ischemia and a trend toward fewer arrhythmias with deferoxamine pretreatment but no improvement in LV function.

The current reported improvement in survival, but not LV function or ATP levels, with deferoxamine pretreatment is consistent with the previous reported studies. Moreover, our study suggests that the important component of deferoxamine therapy lies in its administration before ischemia and that dosing at the time of ischemia may well be redundant. We postulate that pretreatment allows time for this low molecular weight agent to circulate and reach intracellular sites of iron production before ischemia. When present at the time of reperfusion, deferoxamine chelates iron released by injured myocytes during the burst of oxygen-derived free radical production that accompanies reperfusion. This reduces the formation of hydroxyl radicals, thereby preserving surrounding myocardium. Because intracellular passage of deferoxamine is responsible for its effectiveness, improvement in LV function might be realized if the interval between dosing and ischemia was greater. Until this can be tested experimentally, our data suggest that deferoxamine alone is a limited myocardial protectant.

When added to the cardioplegic solution, only one dose of deferoxamine improved survival but not to a statistically significant level. Adenosine triphosphate levels and variables of LV function were not changed. As deferoxamine dose increased, survival tended to be lower. Several other studies, however, have conflicting conclusions. Menasché and co-authors [11], in an ex vivo Langendorff rat heart preparation, reported improved first derivative of LV pressure and LV developed pressure and decreased diastolic pressure after hypothermic global ischemia. These authors later demonstrated the same trends in an ex vivo transplant model when deferoxamine was added to cardioplegia or to the cardioplegia and reperfusate [12]. Illes and associates [18] have reported improved contractility using blood cardioplegia with deferoxamine in an in vivo model of regional ischemia. Ferreira and colleagues [19] administered cardioplegic solution with deferoxamine (1,000 mg/L) to humans undergoing elective coronary artery bypass grafting. Treatment yielded no improvement in clinical outcome or rate of perioperative myocardial infarctions. Although none of these studies is conclusive, there may be a limited dose range of deferoxamine that improves myocardial preservation when administered with cardioplegia. However, as suggested by the current study, concentrations greater than 1 mmol/L may be toxic. Although the present investigation did not test "low-dose" deferoxamine (<0.10 mmol/L), which has been reported to be beneficial [11, 12], at present there is little evidence to support the effectiveness of deferoxamine in improving myocardial preservation when used solely in cardioplegia.

The addition of deferoxamine to the reperfusate seems conceptually and practically inappropriate for myocardial preservation. Few studies have used deferoxamine in the reperfusate alone. Ambrosio and associates [20] have reported an increase in developed pressure, a decrease in compliance, and more rapid and complete recovery of intracellular pH and phosphocreatine using a model of normothermic global ischemia in the isolated rabbit heart model. Yet, even in this model, deferoxamine (50 μmol) was given just before and not exclusively during reperfusion. When deferoxamine therapy was confined to reperfusion in the present study, no statistically significant change in ATP levels, LV function, or survival was found except at the 0.76 mmol/L dose. At this dose, however, survival actually decreased, suggesting the possibility of toxicity.

It has been theorized that deferoxamine has a biphasic dose-response curve, being therapeutic at some doses and toxic at others [17]. The ability of Fe^{2+} and deferoxamine to act as an oxygen radical generating system has been demonstrated [28]. Halliwell [8] has also postulated that if the Fe^{3+}-deferoxamine complex accumulates, reduction could lead to Fe^{2+} release and free radical generation. Deferoxamine has also been shown to keep neutrophils in a prolonged activated state, and high doses have been reported to exacerbate paraquat toxicity in rats by the formation of a paraquat radical that can reduce the deferoxamine-Fe^{3+} complex to a ferrous moiety [29]. The current study supports these theories and suggests that this toxic range is between 0.75 and 1.00 mmol/L. Such doses should be avoided.

We conclude that deferoxamine given intramuscularly 1 hour before ischemia at a dose of 30 mg/kg, and probably 10 mg/kg, significantly improves survival. We postulate that pretreatment allows time for deferoxamine to reach intracellular sites, reducing hydroxyl radical production during ischemia and subsequent reperfusion. The addition of deferoxamine to cardioplegic solution may be beneficial at approximately 0.50 mmol/L, but larger doses may be toxic. Deferoxamine given after ischemia is of little value and may indeed potentiate ischemia-reperfusion injury. Further ex vivo and in vivo studies should concentrate on the use of deferoxamine as a pretreatment agent.

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Familial Cardiac Myxoma

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The majority of cardiac myxomas occur sporadically as isolated lesions in the left atrium of middle-aged women. However, a "familial" form and a "syndrome" form of this lesion have been identified. The syndrome myxoma can present with pigmented skin lesions and peripheral or endocrine neoplasms. The familial and syndrome forms of cardiac myxomas can usually be distinguished from the sporadic form by the presentation at a younger age, the unusual location and multicentricity of the lesions, and the presence of rare pathological conditions. In addition, a higher rate of recurrent lesions is usually associated with the familial and syndrome forms of this disease. To date, 15 families with cardiac myxomas have been reported in the world's literature. Here we present 2 additional case reports.

(Ann Thorac Surg 1992;53:419–24)

The majority of cardiac myxomas occur as a sporadic lesion and are usually found in middle-aged women as an isolated, benign, nonrecurring tumor of the left atrium without accompanying pathological conditions [1]. However, multiple, recurrent, "complex" myxomatous lesions of the heart have been noted with increasing frequency [2]. In addition, a subset of patients with cardiac myxomas in association with pigmented skin lesions and peripheral and endocrine neoplasms has been described [3]. These patients, with "syndrome" myxoma are distinct, as they are younger in age and have a much higher incidence of ventricular, multiple, recurrent, and familial associated cardiac myxomas.

The clinical and pathological features of cardiac myxoma in the syndrome form are similar to those of familial cardiac myxoma. Patients with the latter are again younger in age, they have multiple tumors with frequent involvement of chambers other than the left atrium, and there is a higher incidence of recurrence. Although the exact pattern of hereditary transmission has not been fully elucidated for the familial form, this disorder may represent a continuum of a disease process including a syndrome-associated complex. A review of the world's literature uncovered 15 families with myxoma [4–19]. Here we describe two additional families identified and treated at the University of Florida/Shands Hospital.

Case Reports

Patient 1

A 34-year-old woman was referred to our institution with a recurrent left atrial myxoma discovered during a routine follow-up echocardiogram. The patient's only signs and symptoms were mild shortness of breath and dyspnea on exertion over the last several months. Her surgical history included resection of a right atrial myxoma in 1982, resection of a recurrent right atrial myxoma in 1985, and removal of a left atrial myxoma in 1988. The surgical history also included a bilateral adrenalectomy for pigmented hyperplasia that resulted in Cushing's disease, a total abdominal hysterectomy for leiomyoma, and a thyroid lobectomy for adenoma. In addition, she had sustained a pulmonary embolism in the past. Her family history was notable in that a daughter, maternal uncle, and sister all had cardiac myxoma.

Physical examination revealed a thin woman with marked cutaneous freckles. Cardiac examination revealed a grade 2/6 systolic murmur at the apex radiating to the axilla with an S_4 gallop. A chest roentgenogram demonstrated a new nodule in the right lower lobe.

Two-dimensional echocardiography showed mild mitral valve thickening, mild left ventricular dysfunction, and a 1.5-cm density in the left atrium at the base of the anterior mitral leaflet. A transesophageal echocardiogram produced similar findings (Fig 1). A computed tomogram of the chest revealed the nodule in the right lower lobe to be heterogeneous with areas of calcification.

The patient underwent resection of the recurrent left atrial myxoma through a right anterior thoracotomy. Cannulation for cardiopulmonary bypass was accomplished with placement of the arterial cannula in the right femoral artery and the venous cannulas in both the right femoral vein and the superior vena cava. The lesion was visualized through a left atriotomy and was located at the right anterolateral portion of the left atrium; it extended from the annulus of the anterior mitral valve leaflet up along the aortic portion of the left atrial wall. Resection was accomplished with clear margins, and the endocardial defect was closed primarily. The lesion had a brownish tan appearance and was identified as a hemorrhagic myxoid tumor. The right atrium was explored through a right atriotomy, and no evidence of a recurrent myxoma was noted. A wedge resection of the right lower lobe was also performed and revealed a calcified granulomatous lesion.

The immediate postoperative course was uneventful.

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The patient was discharged from the hospital on the sixth postoperative day. However, she was readmitted to the hospital 2 weeks later for hyperventilation. A ventilation/perfusion scan was suggestive of a pulmonary embolism. She was subsequently anticoagulated and is now doing well.

Patient 2

A 16-year-old boy was seen at an outlying hospital with a 3-month history of nausea, vomiting, weight loss, weakness, and decrease in cognitive function. He had no prior medical history. Of note, both his grandmother and mother had had resection of a cardiac myxomatous lesion in the past. Physical examination showed a cachectic boy with a systolic cardiac murmur, hepatic enlargement, and jugular venous distention to the jaw when he was sitting. The patient also had bilateral heel ulcerations and a sacral decubitus ulcer.

Laboratory values showed marked hyponatremia, hypercalcemia, and hypochloremia. A mild coagulopathy was also noted. Serum cortisol levels were mildly elevated as were the total bilirubin, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and alkaline phosphatase levels. Thyroid function tests revealed mild hypothyroidism. Serological findings for hepatitis A, B, and C were all negative.

Two-dimensional echocardiography revealed a large, lobulated left atrial mass with a stalk attached to the atrial septum that prolapsed into the left ventricle during diastole (Fig 2). The mean pulmonary artery pressure was 50 mm Hg. Moderate tricuspid regurgitation was also noted.

Central hyperalimentation was instituted, and the serum electrolyte values slowly normalized. Broad-spectrum antibiotics were begun with debridement and local wound care of the decubitus ulcers.

After 1 week of medical therapy, the patient underwent resection of the myxomatous lesion through a standard median sternotomy with bicaval venous cannulation for cardiopulmonary bypass. At the time of resection, four distinct lesions were noted, three in the left atrium and a single lesion in the right atrium. After excision of these lesions, a tricuspid valvuloplasty was performed. The postoperative course showed slow but steady improvement in all clinical variables, and the patient was subsequently discharged home. He currently has mild to moderate mitral insufficiency as documented by color-flow transthoracic echocardiography.

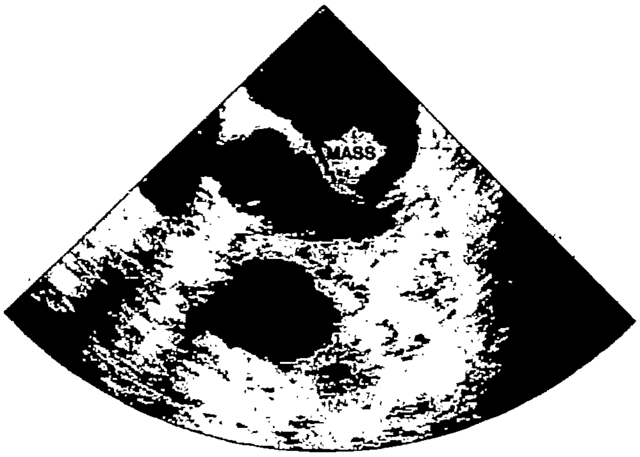

Fig 1. (Patient 1.) Transesophageal echocardiogram showing left atrial mass attached to atrial septum. (AO = aorta; LA = left atrium).

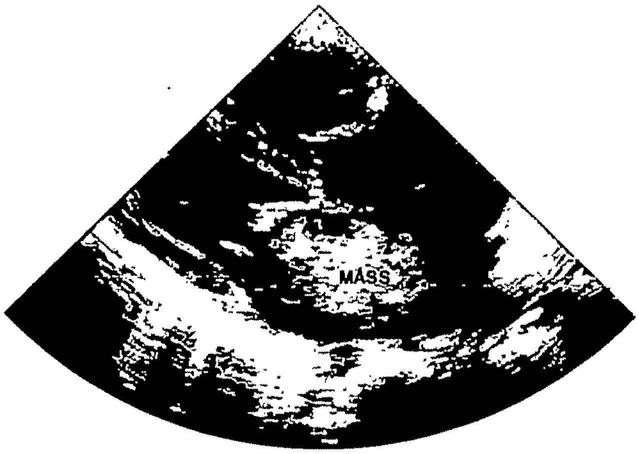

Fig 2. (Patient 2.) Transthoracic echocardiogram showing large left atrial mass. (LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.)

Comment

Most cardiac myxomas occur sporadically and usually are seen in middle-aged women as an isolated tumor in the left atrium without accompanying pathological conditions [1]. However, the literature contains several case reports [4–19] that describe a familial occurrence of this tumor. Also described are associated skin lesions as well as other endocrine tumors [1]. This so-called complex or syndrome form of cardiac myxoma and the familial form have characteristics that distinguish them from the sporadic form. These characteristics include a younger age at presentation, a higher incidence of multiple sites (including the ventricles), and a tendency for recurrence.

Krause and associates [4] described the first cardiac myxoma family in 1971. Since then, 16 other families, including our two, have been identified. The relationships, ages of family members at presentation, tumor locations, methods of diagnosis, presenting symptoms, and description of surgical therapy for all 17 reported families with cardiac myxoma are shown in Table 1.

The familial form of cardiac myxoma is characterized by lesions affecting members of the same family. As in the syndrome form, patients are invariably younger (mean age, 27 years) and have multicentric lesions (22%). The majority of tumors occur in the left atrium (61%), although every cardiac chamber has been involved. More than 10% of patients will have a recurrence. Primary resection was the preponderant form of surgical therapy. Residual atrial defects were repaired either primarily or with a patch. Destruction of a valve resulted in either replacement or annuloplasty.

Inspection of the data in Table 1 suggests a variable hereditary transmission pattern. It had originally been thought that the familial form was transmitted by an autosomal recessive gene with variable environmental factors, as early case reports [4–7] described involvement only in siblings. It now seems likely that the familial form is inherited through an autosomal dominant trait, as the familial form has been documented in parents and their children [8, 11]. A sex-linked recessive inheritance has been ruled out, as the pathological entity has been transmitted from father to daughter. However, no hereditary linkage is well substantiated.

Another hypothesis of transmission involves viral infection with the Coxsackie B4 virus. Immunofluorescent antibody staining and electron microscopic studies have revealed Coxsackie B4 viral antigen and viruslike particles in the cytoplasm of stellate cells of a surgically resected right atrial myxoma [20].

The occurrence of multiple and recurrent lesions has been associated not only with the familial form but also with the syndrome form, or Carney's complex. First described by Carney, the complex form of cardiac myxoma consists of an association with a primary pigmented nodular adrenocortical disease [21]. At least 40 families have been reported with this association. Carney's complex comprises myxomas, spotty pigmentation, and overactivity of the adrenal gland. Several other syndromes have been described. Atherton and associates [22] used the term *NAME* syndrome for *n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and *e*phelides. Rhodes and co-workers [23] presented the case of a patient with a cardiocutaneous syndrome characterized by atrial myxoma, pigmented lesions of the skin and genital mucosa, and opalescent papules and dermal nodules of the skin and tongue. The term *LAMB* syndrome for *l*entigines, *a*trial *m*yxoma, and *b*lue nevi was applied. Thyroid lesions have been noted infrequently with this complex. However, Rhodes was reluctant as of yet to include the thyroid as part of this syndrome.

Familial or complex myxomas may be characterized by the presence of associated skin lesions (ephelides, blue nevi, or lentigines); skin myxomas; myxoid mammary fibroadenomas; Cushing's syndrome, particularly from primary pigmented nodular adrenocortical hyperplasia; pituitary tumors; and testicular (calcifying Sertoli cell tumors), thyroid, and uterine lesions. Hematological disorders include hemolytic anemia and thrombocytopenia. The average age of these patients ranges between 22 and 30 years. Synchronous lesions occur in approximately 50% of patients, and a single lesion is noted in only about one third. The recurrence rate is 21%, and the majority of patients have a primary relative with one or more elements of the complex.

The most common variety of cardiac myxoma is the sporadic form. Several investigators have described a definite set of patient demographics that distinguish the sporadic form from the familial, and syndrome or complex forms [24]. The average age of patients with the sporadic form is greater than 50 years with a mean of 51 years. The vast majority (76%) are women. The lesions are nearly always single (95%), and 76% to 88% occur in the left atrium. Synchronous sporadic myxomas are particularly rare (1%), and the risk of recurrence is less than 1%.

Several studies have documented similar clinical manifestations at presentation for the nonfamilial and familial cardiac myxomas. All the familial neoplasms were discovered because of symptoms and not as a result of screening evaluations conducted with the relatives of affected patients. In fact, several members of families with the syndrome had normal cardiac evaluations initially and only later had development of cardiac myxomas. Other family members with nonspecific complaints were suspected of having myxomatous lesions after another affected family member was identified.

The hallmark of an atrial myxoma is an enigmatic presentation of intermittent and variable cardiac signs frequently combined with vague and constitutional abnormalities. Certain aspects of these tumors that should make one suspect the familial or syndrome form of myxomatous disease include the presence of lesions in the right atrium, calcification, valve destruction, hematological abnormalities including hemolytic anemia and thrombocytopenia, and occurrence in children [9].

Although distal myxomatous emboli have been described, particularly to the brain [25], lungs [26], and peripherally, such myxomatous embolic fragments rarely grow into secondary deposits. One such report [27] involves spread to the humerus. It is known that myxomatous embolization does occur; however, vascular invasion by myxomatous emboli is highly unlikely in view of the benign histology. Indeed, there is no detectable difference histologically between familial and nonfamilial myxomas [9].

Myxomas can recur at the site of the original tumor, at multiple intracardiac sites, and at sites outside the heart. Recurrences can occur more than once after surgical excision. It is uncertain whether they are due to a multicentric origin of the initial lesion, inadequate resection of the lesion, intracardiac implantation, peripheral embolization, or a combination of these factors [17].

In conclusion, cardiac myxomas are the most common form of primary cardiac tumors. Several forms of this pathological entity have been delineated. Familial and syndrome forms can be distinguished from the sporadic form and should be suspected on the basis of clinical findings including the patient's age, sex, cardiac chambers affected, number of tumors found, and presence or absence of accompanying disorders. Family members of affected patients should be screened periodically with echocardiography in an attempt to identify asymptomatic cardiac myxomas. To date, 17 families with cardiac myxoma have been identified. However, this may represent only part of a spectrum including patients with the syndrome form who have part but not all of the associated constellation.

Any patient less than 40 years of age with a cardiac myxoma at a site other than the left atrium should be suspected of having a syndrome form of myxoma. The integrity of the adrenal gland should be confirmed preoperatively, and routine intraoperative inspection of the

Table 1. Reported Cardiac Myxoma Families, 1971 to 1991

	Relation	Age (y)	Location	Diagnosis	Presentation	Surgical Therapy
Krause et al	Brother^a	25	LA	Autopsy	. . .	. . .
[4], 1971	Brother^a	37	RVOT	Cath	Fever, psychosis, cough	Resection, PVR
Liebler et al		42	LA	Cath	Orthopnea, cough	Died before operation
[7], 1976	Brother^a	34	RA,^{b} RV, LA	Cath	Murmur, chest pressure	Resection
	Brother^a	46	RV, LA	Cath/echo	Murmur, previous CVA	Resection
Kleid et al	Brother	14	LA	Cath/echo	Peripheral emboli, murmur	Resection
[5], 1973	Brother	16	RA	Cath/echo	Fever, weakness, murmur	Resection
Farah [6],	Brother	21	RA	Cath	Fever, arthralgia, murmur	Resection
1975	Sister	30	LA	Cath/echo	Murmur, cerebral aneurysms	Resection
Siltanen et al	Mother	32	RA, LA	Cath	Fever, arthralgia, murmur	Resection
[8], 1976	Son	12	LA	Cath	Femoral emboli	Resection
	Son	20	RA	Cath/echo	Fatigue, palpitations	Resection, TVR
	Son	18	LA	Cath/echo	Murmur, hemiplegia, aphasia	Resection
Crawford et al	Mother	?	LA	Autopsy	. . .	. . .
[9], 1978	Daughter	12	RA	Cath	Dyspnea, peripheral edema	Resection, TVR
Laboux et al	Brother^c	23	RV	Cath/echo	Asymptomatic murmur	Resection
[10], 1978	Brother^c	23	RV	Cath/echo	Dyspnea on exertion, murmur	Resection
Powers et al	Father	48	RA^b	Cath/echo	Fever, malaise, sore throat	Resection
[11], 1979	Daughter	19	RVOT	Cath/echo	Murmur, fever, headache	Resection
Proppe and Scully [12], 1980	Brother	16	LV	Autopsy	Large-cell calcifying Sertoli cell tumor of testis	. . .
	Brother	10	LA	Autopsy	Large-cell calcifying Sertoli cell tumor of testis	. . .
Tway et al	Sister	25	RA, LA^b	Echo	Asymptomatic murmur	Resection, ASD repair
[13], 1981	Sister	13	LA	. . .	. . .	Resection
Schweizer-Cagianut	Brother	4	LA	Autopsy	Failure to thrive	. . .
et al [14], 1982	Sister	36	LA	Autopsy	Lentiginosis, primary adrenocortical nodular hyperplasia	. . .
Grauer and Grauer	Father	56	LA	Echo	Malaise, TIA, V tach	Resection
[15], 1983	Daughter	16	LA	Cath	Splenic infarct	Endothelial stripping
		18	LA	Cath	Cerebral infarct, hemiparesis	Endothelial stripping
		20	RA, LA	Cath	Pneumonia	Resection
		29	RA	Cath	. . .	Resection, atrial septectomy
Richter et al	Mother	49	LA	Echo	Peripheral emboli, paresis	Resection
[16], 1985			LA	Echo	. . .	Resection
	Daughter	17	LA	Echo	. . .	Resection, ASD repair
Gray and Williams	Sister	?	LA	Autopsy	. . .	. . .
[17], 1985	Sister	18	LA	Cath	Fatigue, dyspnea, hemoptysis	Resection
		29	LA, RA	Cath	Murmur, arm claudication	Resection, ASD repair
		42	RV, TV, LA	Cath/echo	Dyspnea, malaise, murmur	Resection, TVR, ASD repair
Schuiki and Hedinger [18], 1987	Mother	64	LA	Autopsy	CVA, primary adrenocortical nodular dysplasia	. . .
	Son	33	LA	Echo	Asymptomatic; cutaneous nodules	Resection

Table 1. Continued

	Relation	Age (y)	Location	Diagnosis	Presentation	Surgical Therapy
Pagola-Caltasco et al [19], 1989	Mother	42	LA[b]	Cath/echo	Peripheral edema, dyspnea	Resection
	Son	14	RV	Cath/echo	Angina, peripheral edema	Resection
van Gelder et al [present study], 1992	Woman	26	RA	Echo	Dyspnea, syncope	Right atrioplasty
		29	RA	Echo	Pulmonary embolus	Resection
		32	LA	Echo	Dyspnea, fatigue	Resection
		34	LA	Echo	Adrenocortical nodular hyperplasia	Resection
	Daughter	8	LA	Autopsy	Cough, headache	. . .
	Sister	31	RA	Echo	Stroke	Resection
	Uncle	46	LA	Autopsy	Esophageal psammatous melanotic schwannoma, pigmented adrenocortical disease	. . .
	Boy	16	LA,[b] RA	Cath/echo	Cognitive changes, cachexia	Resection, tricuspid valvuloplasty
	Mother	38	RA, LA[b]	Echo	Stroke, weight loss	Resection
	Grandmother	56	LV	Cath	Bell's palsy, weight loss	Died during operation

[a] These brothers were in the same family. [b] Multiple tumors were present. [c] These brothers were twins.

ASD = atrial septal defect; Cath = cardiac catheterization; CVA = cerebrovascular accident; Echo = echocardiography; LA = left atrium; LV = left ventricle; PVR = pulmonary valve replacement; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; TIA = transient ischemic attack; TV = tricuspid valve; TVR = tricuspid valve replacement; V tach = ventricular tachycardia.

other cardiac chambers for multiple subclinical myxomas should be conducted. Any patient with familial, recurrent, or multicentric cardiac myxomas combined with cutaneous pigmentations or peripheral noncardiac myxomas should be followed up closely for recurrent disease.

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Adverse Hemodynamic Effects of Pericardial Closure Soon After Open Heart Operation

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The short-term hemodynamic effects of pericardial closure on cardiac function were studied during steady-state anesthesia and ventilation in 10 patients (6 men) (mean age, 59 ± 9 years) who underwent an open-heart valve operation. Observations were made after the heart was decannulated, both while the pericardium was open and after it had been closed, and then after closure of the chest after the pericardium had been reopened by removing the pericardial suture through the chest wall. The effect of closing the pericardium before closing the chest was an immediate reduction in cardiac output (thermodilution) of 1.39 ± 0.24 L/min from 5.09 ± 0.40 L/min ($p < 0.001$). The heart rate remained stable, but there was a decrease in stroke volume of 29% and an increase in systemic vascular resistance of 34% (both, $p < 0.01$). The mean arterial pressure increased slightly by 2% (not significant). Opening the pericardium (1.5 to 2 hours after the end of the operation) while the chest remained closed was followed by an increase in cardiac output of 1.33 ± 0.15 L/min from 4.12 ± 0.62 L/min ($p < 0.001$). As the heart rate and the mean blood pressure changed insignificantly, there was an increase in stroke volume of 15 ± 3 mL from 53 ± 5 mL and a reduction in systemic vascular resistance of 473 ± 83 dyne · s · cm^{-5} from 1,721 ± 181 dyne · s · cm^{-5} (both, $p < 0.01$). The data suggest that pericardial closure early after an open heart operation consistently lowers stroke volume and cardiac output; mean blood pressure is maintained by an increase in systemic vascular resistance. Thus, monitoring blood pressure alone is not a reliable guide to decisions on whether to close the pericardium or leave it open in individual patients.

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The physiological function of the intact pericardium with its fluid is to lubricate and isolate the heart from other structures in the thorax, thus preventing adhesions and the spread of infection [1]. Congenital absence of the pericardium or surgical removal, however, has no serious effects [2]. Traditionally surgeons were against closure of the pericardium after an open heart operation in the belief that this would increase the risk of tamponade [3]. More recent studies have suggested, however, that closure of the pericardium may reduce postoperative bleeding [4, 5] and protect the heart at repeat sternotomy [6]. Controversy remains regarding the effects of pericardial closure on cardiac function, particularly on blood pressure and cardiac output. Reduction in cardiac output [7–9] and blood pressure [10] has been reported after pericardial closure. All these studies [7–10] included patients who had undergone coronary artery bypass grafting, and consequently there was the possibility of a constrictive effect of pericardial closure on the grafts as well as on the heart. In the work of Damen and Bolton [10], measurements were carried out only intraoperatively while the sternotomy remained opened, a situation that may not be directly relevant to the clinical status after chest closure.

In a recent study in pigs, our group [11] showed that after sternotomy and pericardiotomy, pericardial closure consistently lowered cardiac output and stroke volume, whereas systemic blood pressure was maintained by an increase in systemic vascular resistance. These changes were reversed by opening the pericardium. However, no cardiac operation was performed, and extrapolation of animal data to humans cannot be absolute. The aim of the present study was, therefore, to assess the hemodynamic effects of closing and opening the pericardium while the chest remained open and after it had been closed in 10 patients who underwent a valve operation.

Material and Methods

With informed consent, studies were performed on 10 patients who required a valve procedure. There were 6 male patients, and the mean age was 59 ± 9 years (± standard deviation). Six patients underwent mitral valve replacement, 3 had aortic valve replacement, and 1 had mitral valve repair and annuloplasty. Anesthetic and operative techniques were standardized. Throughout the study period, the patients did not receive vasopressor, vasodilator, or inotropic pharmacological agents.

Hemodynamic Measurements

A peripheral electrocardiographic lead was monitored in the usual manner, and the heart rate was recorded. A

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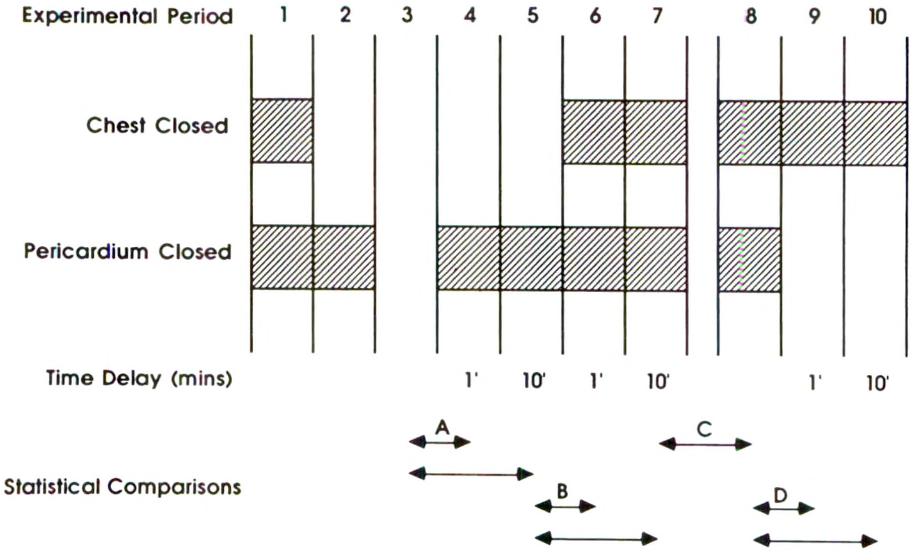

Fig 1. The study protocol. The cross-hatched areas represent the experimental periods during which the chest, the pericardium, or both were closed. During period 3, the open heart procedure was performed. Between periods 7 and 8, the patient was transferred from the operating theater to the cardiac intensive care unit. The lines at the foot of the figure denote the periods used for the statistical comparisons. (A = pericardial closure with the chest open (periods 4 and 5 versus period 3); B = chest closure with the pericardium closed (period 7 versus period 5); C = comparison between period 8 and period 7 (time delay between these periods was 1.5 to 2 hours [see text]); D = pericardial opening with the chest closed (periods 9 and 10 versus period 8).)

20-gauge Jelco cannula (Critikon Ltd, Tampa, FL) was placed percutaneously into a radial artery for continuous measurement of blood pressure (Viggo/Spectramed pressure transducers; BOC Health Care Co, Swindon, Wiltshire, UK) and for sampling of blood for arterial gases. The tip of a 7F Swan-Ganz flow-directed thermodilution catheter (Baxter International Inc, Santa Ana, CA) was positioned in the pulmonary artery through a percutaneous internal jugular venotomy. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were recorded, and cardiac output was measured in duplicate (or in triplicate if the difference between the first two measurements was > 10%) using an SAT 1 oximeter/cardiac output computer (American Edwards Laboratories, Santa Ana, CA). Stroke volume and systemic and pulmonary vascular resistances were calculated using standard formulas [12].

Experimental Protocol

A maximum of ten sets of data were recorded for each patient, as summarized in Figure 1. Baseline hemodynamic measurements were recorded with the chest closed (period 1), and then after the chest was opened through a median sternotomy, the measurements were repeated (period 2). The pericardium was opened through a vertical incision, after which the measurements were again repeated (period 3).

The operative procedure was performed during period 3. The mean cardiopulmonary bypass time was 81 ± 5 minutes, with a mean aortic cross-clamp time of 44 ± 5 minutes. After decannulation, 20 minutes were allowed to elapse so that a stable state was reached before the hemodynamic measurements were repeated. The pericardium was then closed using a continuous 1-0 Ethilon suture (Ethicon Ltd, Edinburgh, UK), which was exteriorized at each end of the skin wound. The ends of the suture were secured to the surgical drapes to keep the pericardium tightly closed. Sets of data were recorded 1 minute and 10 minutes later (periods 4 and 5, respectively). The sternotomy incision was then closed in layers, and further sets of data were recorded at 1 minute and 10 minutes (periods 6 and 7).

With the ends of the pericardial suture taped securely to the skin, the patient was transferred from the operating theater to the cardiac intensive care unit. With the patient in a steady state of anesthesia and ventilation, the hemodynamic measurements were repeated (period 8). The time between periods 7 and 8 was a mean of 105 minutes (range, 90 to 125 minutes). Then, while the chest remained closed, the pericardium was opened by pulling out the pericardial suture, and sets of data were recorded at 1 minute and 10 minutes (periods 9 and 10, respectively). In the first 5 patients, radiopaque metal clips were applied to the edges of the pericardium. A chest roentgenogram was obtained to confirm that the pericardium remained closed until the suture was removed and again to confirm that the edges became widely separated when it was withdrawn.

The most important variables after four key interventions are summarized in Figure 2. These interventions were pericardial closure with the chest open (data set A, corresponding to the changes between periods 4 and 5 compared with period 3 in Fig 1), chest closure with the pericardium closed (data set B, periods 6 and 7 compared with period 5), transfer of the patient from the operating theater to the cardiac intensive care unit with both chest and pericardium closed (data set C, period 8 compared with period 7), and pericardial opening while the chest remained closed (data set D, periods 9 and 10 compared with period 8).

Statistical Analysis

Data are expressed as the mean ± the standard error of the mean unless stated otherwise. In Figure 2, data are given as mean changes compared with the value preceding the intervention. The statistical significance of the

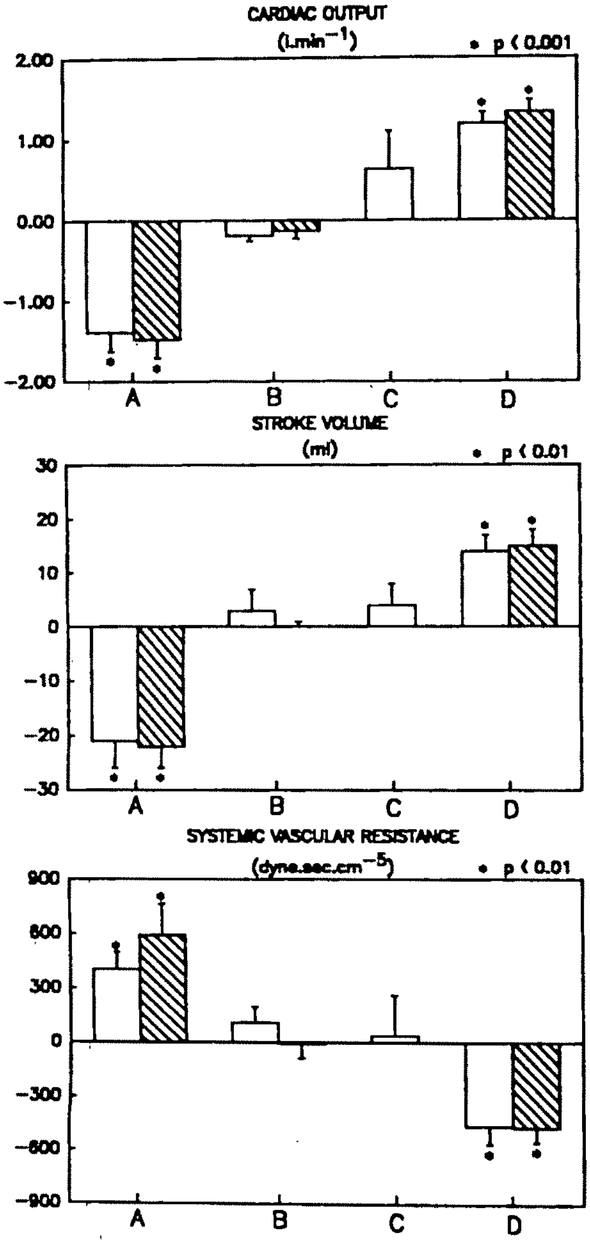

Fig 2. Summary of mean changes (± standard error of the mean) in cardiac output, stroke volume, and systemic vascular resistance during four key periods of study. Open bars *are change at 1 minute and* hatched bars, *change at 10 minutes. The statistical comparison is with the value preceding the intervention. (A = pericardium closed, chest open; B = pericardium closed, chest closed; C = transfer from operating theater to cardiac intensive care unit; D = pericardium open, chest closed.)*

changes in the measured variables was determined by using paired Student's *t* tests. The overall level of significance was set at a probability equal to 0.05 for two-tailed tests.

Results

When the chest was opened by median sternotomy, there were no significant hemodynamic changes: heart rate, right atrial pressure, mean pulmonary artery pressure, and stroke volume remained constant; cardiac output fell insignificantly by 2%; and mean arterial pressure and calculated systemic vascular resistance rose insignificantly by 2% and 3%, respectively. Pericardiotomy caused a rise in heart rate of 3 ± 1 beats per minute from 62 ± 4 beats per minute and in cardiac output of 0.04 ± 0.05 L/min from 3.43 ± 0.10 L/min. Mean arterial pressure fell by 2 ± 3 mm Hg from 76 ± 4 mm Hg; systemic vascular resistance, by 59 ± 65 dyne · s · cm^{-5} from 1,651 ± 98 dyne · s · cm^{-5}; and stroke volume, by 2 ± 1 mL from 56 ± 2 mL. None of these changes were significant. There were no changes in the right heart pressures.

After discontinuation of cardiopulmonary bypass, closing the pericardium while the chest remained open caused an immediate reduction in cardiac output of 1.39 ± 0.24 L/min from 5.09 ± 0.40 L/min ($p < 0.001$) (Table 1). There was no further change after 10 minutes (see Fig 2, data set A). As the heart rate remained stable (75 ± 5 to 74 ± 4 beats per minute), there was a decrease in stroke volume of 21 ± 5 mL from 72 ± 8 mL ($p < 0.01$). There was no initial change in mean arterial pressure 1 minute after closure of the pericardium, but there was an insignificant increase of 5 ± 3 mm Hg from 76 ± 5 mm Hg after 10 minutes. The central venous pressure (right atrial) remained unchanged at 6 ± 1 mm Hg. Systemic vascular resistance increased by 400 ± 95 dyne · s · cm^{-5} from 1,193 ± 147 dyne · s · cm^{-5} ($p < 0.01$). There were no changes in mean pulmonary artery pressure or in calculated pulmonary vascular resistance after pericardial closure.

Closing the chest caused no major change in any of the hemodynamic variables (see Table 1; Fig 2, data set B). Immediately after the chest was closed, the heart rate fell slightly (by 11%), and the mean arterial pressure increased slightly (by 5%), but neither was significant; however, after 10 minutes, both approximated the values recorded after pericardial closure (see Table 1).

After the patients were transferred from the operating theater to the cardiac intensive care unit, there was an increase in cardiac output of 0.64 ± 0.47 L/min from 3.48 ± 0.19 L/min (see Fig 2, data set C). There was also a slight increase in heart rate (by 3%), mean arterial pressure (by 8%), stroke volume (by 10%), and systemic vascular resistance (by 2%), but none were significant (see Table 1). There was no change in the pressures of the right side of the heart.

Opening of the pericardium while the chest remained closed was followed by an immediate and persistent rise in cardiac output of 1.19 ± 0.14 L/min from 4.12 ± 0.60 L/min ($p < 0.001$) (see Fig 2, data set D). Because there was an insignificant increase in heart rate from 77 ± 5 beats per minute to 81 ± 5 beats per minute, there was a corresponding increase in stroke volume of 14 ± 3 mL from 53 ± 5 mL ($p < 0.01$). Mean arterial pressure did not change, and calculated systemic vascular resistance fell by 464 ± 99 dyne · s · cm^{-5} from 1,721 ± 181 dyne · s · cm^{-5} ($p < 0.01$). These changes all persisted during the 10 minutes after the pericardium had been opened (see Table 1). There was no change in the right heart pressures or the pulmonary vascular resistance.

Table 1. Hemodynamic Measurements During Each Study Period[a,b]

	Period							
Variable	3	4	5	6	7	8	9	10
Heart rate (beats/min)	75 ± 5	74 ± 4	76 ± 5	68 ± 4	75 ± 5	77 ± 5	81 ± 5	83 ± 6
Mean arterial pressure (mm Hg)	76 ± 5	77 ± 4	81 ± 4	85 ± 3	79 ± 4	85 ± 2	84 ± 3	84 ± 3
Cardiac output (L/min)	5.09 ± 0.4	3.7 ± 0.27^c	3.6 ± 0.23^c	3.43 ± 0.24^c	3.48 ± 0.19^c	4.12 ± 0.6	5.31 ± 0.6^d	5.45 ± 0.62^d
Stroke volume (mL)	72 ± 8	51 ± 4^e	49 ± 5^e	52 ± 5^e	48 ± 4^e	53 ± 5	67 ± 6^f	68 ± 7^f
Systemic vascular resistance (dyne · s · cm^{-5})	1,193 ± 147	$1{,}593 \pm 134^e$	$1{,}692 \pm 126^e$	$1{,}802 \pm 118^e$	$1{,}684 \pm 118^e$	1,721 ± 181	$1{,}257 \pm 96^f$	$1{,}248 \pm 115^f$

[a] Periods 3 to 10 are as described in Figure 1. [b] Data are shown as the standard error of the mean. [c] Significance: $p < 0.001$ versus period 3. [d] Significance: $p < 0.001$ versus period 8. [e] Significance: $p < 0.01$ versus period 3. [f] Significance: $p < 0.01$ versus period 8.

Comment

This study showed that pericardial closure lowered cardiac output irrespective of whether the chest was open or closed. Heart rate and mean arterial pressure remained constant because of an immediate elevation of the systemic vascular resistance, which was maintained after the chest was closed. The reversal of these effects was observed when the pericardium was reopened. This is in agreement with data from our animal model [11], in which the use of a small epicardial echocardiographic probe enabled us to demonstrate an increase in the size of the left ventricle when the pericardium was opened, a finding compatible with constriction of the heart chamber as the underlying cause of the hemodynamic changes induced by pericardial closure. Such a restrictive effect may be greater after the period of cardiopulmonary bypass and cardioplegic arrest when some degree of edema to the heart is to be expected. This may be further enhanced by the presence of chest drains and residual blood in the pericardial cavity.

Between the last measurement in the operating theater and the first in the cardiac intensive care unit, a mean time of 105 minutes lapsed during which there was no major compensation of the depressed cardiac output or stroke volume. These results compare favorably with those in previous studies [7, 8] in which a continuous suture was withdrawn through the chest wall 11 to 15 hours after the sternum had been closed. They suggest that the depression in cardiac output and stroke volume is not temporary but persists as long as the pericardial closure exerts a restrictive effect on the heart.

A previous report of hypotension after pericardial closure [10] was not confirmed in this study. This may be explained by differences in study design. Propranolol hydrochloride was used in the cardioplegic solution, and this may have had an effect on the systemic blood pressure. Also, the effect of pericardial closure was assessed only intraoperatively while the sternotomy remained opened. Furthermore, the study included patients who underwent coronary artery bypass grafting, in whom pericardial closure may have had a constrictive effect on the grafts as well as on the heart, although there was no report of electrocardiographic evidence of ischemia. The design of our study, in which only patients who had had a valve procedure were entered, allowed us to avoid the confounding influences caused by the presence of bypass grafts.

The fact that the rapid fall in cardiac output and stroke volume resulted in an increase in systemic vascular resistance, which maintained arterial blood pressure, may be an argument for closing the pericardium in patients who remain in stable condition and in a good circulatory state as they come off bypass. However, even in these patients, a reduction in cardiac output and an increase in peripheral systemic vascular resistance may reduce peripheral perfusion, cause acidosis, and slow the rate of rewarming after operation.

In conclusion, this study suggests that measuring systemic arterial blood pressure and other simple hemodynamic indices is insufficient to demonstrate the circulatory effect of pericardial closure in individual patients. Any decision as to whether or not to close the pericardium can be made in the operating theater while the chest is still open by measuring the effect of closure on cardiac output and systemic vascular resistance. In the critically ill patient with a low cardiac output, poor peripheral perfusion, or other problems when coming off bypass or who already requires inotropic support, any further acute embarrassment to the circulation should be avoided by leaving the pericardium open.

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Early Results of Direct Repair of Aortic Interruption by the Lateral Approach

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Eleven consecutive patients were operated on for interruption of the aortic arch by direct aortoplasty through a lateral approach. Median age was 5 days and median weight, 3.52 kg. All received prostaglandin E. Four of the 11 required preoperative ventilatory and inotropic support. Diagnosis was by echocardiography with one confirmed by angiography. There were five type B and six type A interruptions. Aortic continuity was achieved through a left thoracotomy. The aorta and great vessels were mobilized, and after clamps were placed above and below the interruption, ductal tissue was excised and direct anastomosis performed. There was one death from sepsis. One patient died of pulmonary hypertension early after the second operation for correction of other anomalies, and 1 died of hypoplastic lungs after 6 months of ventilation. In 10 of the 11 patients there was no postoperative gradient. Palliative staged approach for correction of this malformation is advocated. The need for bypass and profound hypothermia is removed. This approach restores aortic continuity without sacrifice of the major vessels, use of ductal tissue, or use of prosthetic grafts that will necessitate reoperation.

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Interrupted arch is defined as complete loss of continuity between the ascending and descending portions of the aorta. It is a rare congenital defect that usually arises in association with other cardiac malformations, notably ventricular septal defect and left ventricular outflow tract obstruction. Survival of the children affected is dependent on a patent ductus arteriosus. The etiology of the condition is thought to result from a large ventricular septal defect that causes preferential shunting of blood from the ascending aorta into the pulmonary artery leading to a reduction in flow through the developing aorta and a predisposition to either arch interruption or severe coarctation [1]. There are three types of arch interruption: type A = interruption between the left subclavian artery and the ductus (43%); type B = interruption between the left subclavian and left common carotid arteries (53%); and type C (the least common; 4%) = interruption between the innominate and left common carotid arteries (Fig 1) [2].

For editorial comment, see page 369.

If interrupted arch is left uncorrected, nearly all patients will die during the first year of life [3]. The results of treatment of this condition and the associated defects remain disappointing. There are three methods advocated for the surgical correction of interrupted arch. The first is a one-stage correction through a median sternotomy using cardiopulmonary bypass, deep hypothermia, and circulatory arrest to correct all malformations. The second is reconstruction of the arch with a prosthetic tube graft and correction of the remaining abnormalities at a second operation. The third is direct reconstruction of the arch through a left thoracotomy and again subsequent repair of the associated abnormalities on cardiopulmonary bypass. It is our experience with the third option that we describe here.

Material and Methods

Patient Population

Between 1988 and 1990, 11 consecutive patients, 5 female and 6 male neonates, were operated on by direct aortoplasty through a lateral approach. Median age at operation was 5 days (range, 1 to 16 days), and median weight at operation was 3.52 kg (range, 2.46 to 4.58 kg). All patients received prostaglandin infusions preoperatively to maintain patency of the ductus arteriosus. Four of the 11 required ventilatory and inotropic support before operation.

The diagnosis of arch interruption was made by echocardiography in all instances. There were five type B and six type A interruptions; no type C malformations were found. Associated cardiac anomalies included ventricular septal defect, atrial septal defect, aortopulmonary window, subaortic obstruction, and bicuspid aortic stenosis. Associated noncardiac malformations included DiGeorge syndrome, talipes equinus, and hypoplastic lungs. All operations were carried out by one surgeon (R.B.).

Operative Technique

An arterial pressure monitoring catheter is placed in the right arm before the procedure, and an oxygen saturation monitor is placed on the left hand. The chest is entered through a left anterolateral thoracotomy in the fourth intercostal space. The lung is retracted anteriorly and

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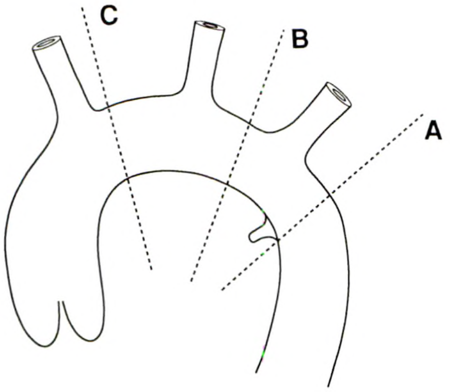


Fig 1. The three types of aortic arch interruption.

downward. The superior intercostal vein is ligated and divided. The mediastinal pleura is incised longitudinally and reflected to expose the arch, left subclavian artery, ductus, and descending thoracic aorta. Tapes are passed around all the major structures involved in the dissection.

All vessels are fully mobilized without damaging or sacrificing any intercostal arteries. Care is taken not to damage the recurrent laryngeal and phrenic nerves. The descending aorta is mobilized down to the diaphragm. This extensive mobilization of the descending aorta is only possible through a left thoracotomy. By the end of the dissection, the intercostal arteries that normally run laterally and upward from the descending aorta run laterally and downward.

The ascending aorta, proximal arch, and cranial vessels are likewise fully dissected free of adventitia and fully mobilized. In patients with large left-to-right shunts, the pulmonary artery is often larger than the ascending aorta. In these patients, access is improved by opening the pericardium anterior to the left phrenic nerve. If the pulmonary artery is to be simultaneously banded, which was done in 2 patients, this step becomes essential.

The ductus is then divided, and distal bleeding is controlled by the application of a spoon-shaped clamp on the descending aorta. A second vascular clamp is placed to control the proximal arch, the left subclavian artery (depending on the type of interruption), and the left common carotid artery and to partially occlude the innominate artery (Fig 2). If the pressure measured in the right arm is greater than 50 mm Hg, we consider the cerebral circulation protected and hence thought it safe to proceed in 10 of 11 patients. The size of the ascending aorta in the region of the bifurcation was estimated at the time of operation to be between 6 and 10 mm.

All visible ductal tissue is completely excised from the distal segment. An incision is made on the undersurface of the arch and extends proximally to the ascending aorta and distally to the left common carotid artery when necessary. In 10 of the 11 patients, the aorta was large enough to apply the proximal clamp at the bifurcation for a satisfactory direct anastomosis, but in 1 patient with type B interruption, the pressure in the right arm was less than 50 mm Hg when the clamp was placed. Therefore, the clamp was reapplied mainly across the left common carotid artery, the underside of which was used for the direct anastomosis.

The two vascular clamps were then approximated, allowing the proximal and distal segments to be anastomosed using continuous 7-0 Prolene (Ethicon, Somerville, NJ) without tension [4]. After completion of the anastomosis, the vascular clamps are removed, the distal one first. The thoracotomy is then closed in the routine manner.

Results

All 11 patients survived the initial procedure. There were no complications from bleeding. Two patients sustained perioperative convulsions from which they made a complete recovery without residual neurological abnormalities. In 10 of the 11 patients, no gradient or only a negligible gradient across the aortoplasty was detected at postoperative investigation (Figs 3, 4).

All surviving patients with the exception of the patient with subaortic obstruction have undergone subsequent correction without any deaths. Follow-up ranges from 6 months to 3 years. No patient has any evidence of residual aortic obstruction.

There were three deaths. One infant survived the initial operation and subsequently required balloon valvuloplasty to a stenotic bicuspid aortic valve. After successful valvuloplasty, a bilateral chylothorax developed associated with traumatic insertion of an internal jugular line. The chylothorax was successfully managed by ligation of the thoracic duct at the diaphragm, but the infant died of sepsis 11 days after balloon valvuloplasty.

In another infant, the initial procedure involved direct anastomosis between the descending aorta and the left carotid artery to restore aortic continuity, as the diameter of the ascending aorta was small (6 mm). The pulmonary artery was banded at the same time. This patient was the only 1 in whom there was a demonstrable gradient across the repair. The patient was discharged home but was readmitted soon after with heart failure. At the second operation, the pulmonary artery band was found to be

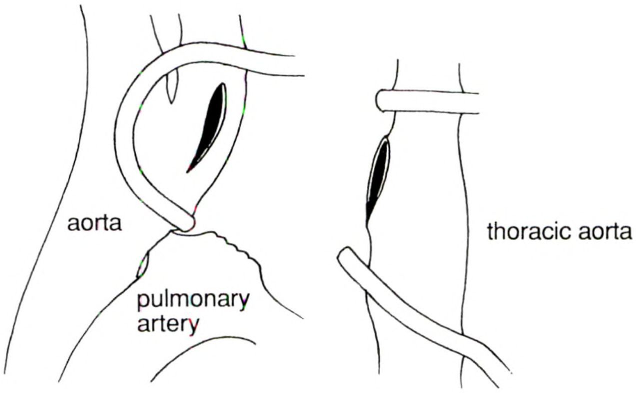
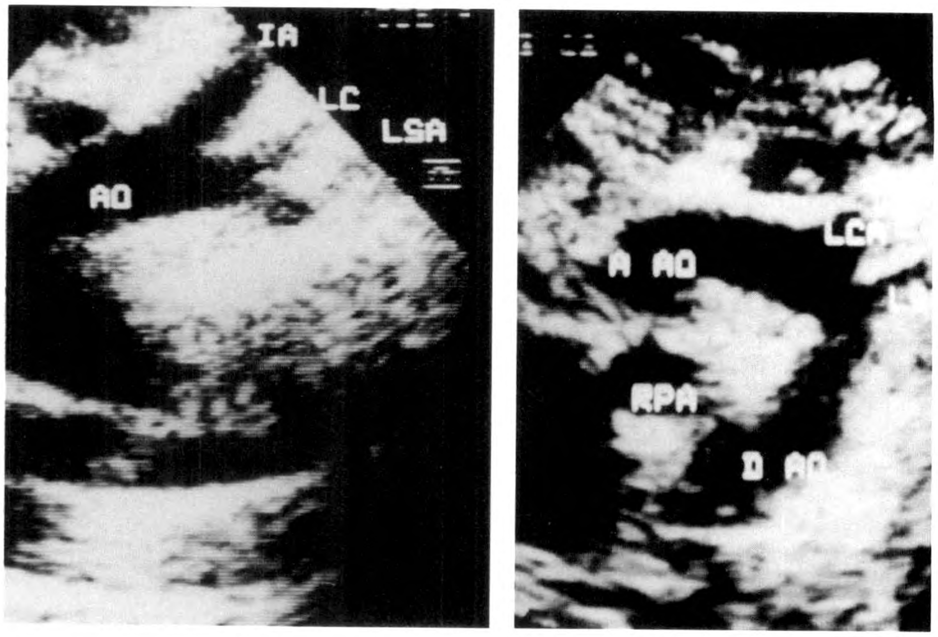


Fig 2. Position of vascular clamps on arch and descending aorta before fashioning of anastomosis.



A B

Fig 3. Two echocardiograms showing perioperative anatomy: (A) before and (B) after surgical correction. (AO = *aorta;* A AO = *ascending aorta;* D AO = *descending aorta;* IA = *innominate artery;* LC, LCA = *left common carotid artery;* LSA = *left subclavian artery;* RPA = *pulmonary trunk.)*

loose, the ventricular septal defect was closed, and the arch was enlarged by the use of a pericardial patch. The infant died of a pulmonary hypertensive crisis in the early postoperative period.

The third patient who died had known pulmonary hypoplasia, and death occurred late after arch repair. Repeated echocardiograms did not demonstrate any residual gradient across the repair, but the patient could not be weaned from the ventilator. The hemodynamic state of the patient was corrected by repairing the ventricular septal defect. During the prolonged period of ventilation for 6 months there was no evidence of lung growth, and eventually the patient died of septicemia, disseminated intravascular coagulation, and renal failure.

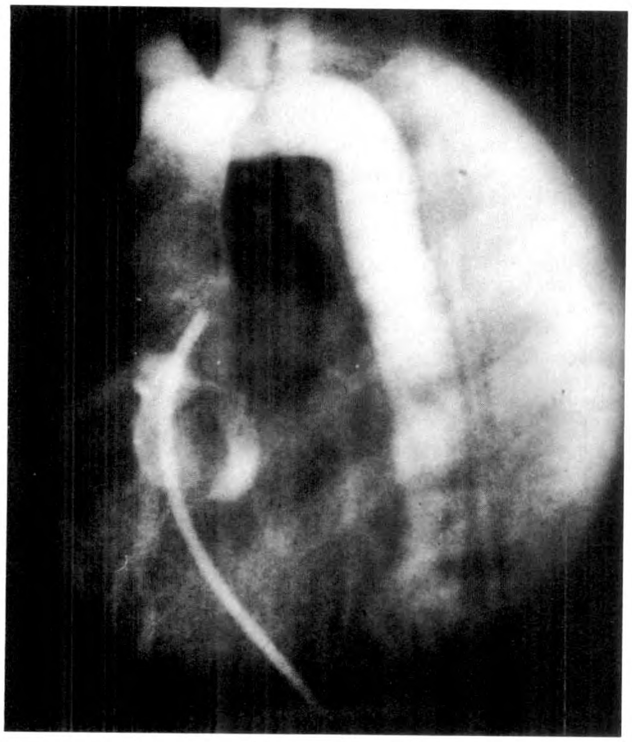


Fig 4. Postoperative aortogram showing successful restoration of aortic continuity.

Comment

Interruption of the aortic arch accounts for about 1% of all congenital heart disease. The condition can remain asymptomatic until the ductus arteriosus closes. This is followed by left ventricular strain and then failure as the condition of the infant rapidly deteriorates, and results in a very high mortality in early life [3]. The introduction of prostaglandin infusions has made it possible for most of these infants to undergo surgical intervention [5]. In our series, all patients were treated in this manner before operation. Diagnosis was made in all patients by echocardiography and was further confirmed in only 1 by angiography, which is in line with previous experience from other series [5–7]. Cardiac catheterization was avoided, as it is an independent risk factor for early survival after operation [8].

The first successful one-stage correction of aortic arch interruption and the associated cardiac anomalies was reported in 1970 by Singh and colleagues [9]. This approach has been advocated by several authors [10–14] since then. One-stage correction can be attempted through one incision (Bailey and co-workers [11] described an approach through a large transverse incision) or two incisions performed consecutively at the same operation. All one-stage procedures require cardiopulmonary bypass to repair the intracardiac anomalies, and in the neonatal period, this is frequently complicated by pulmonary and renal dysfunction. Full mobilization of the descending thoracic aorta is difficult with a median sternotomy, and for anastomosis, hypothermic circulatory arrest is essential. This method, although a well-accepted technique, has the additional problem of potential cerebral damage. It is questionable whether procedures of this magnitude should be performed on neonates when a palliative procedure to the aorta may allow time for growth before a final correction of the other intracardiac abnormalities. In a series from Liverpool [8], the early mortality of patients who underwent a palliative repair was less than half that of patients having total one-stage correction.

The most suitable technique for the restoration of aortic continuity is controversial. There are three options: prosthetic conduit, subclavian/carotid interposition, or direct end-to-end aortic anastomosis. The use of prosthetic conduits to either bypass or replace the interrupted segment was first described by Van Praagh and co-workers [15] in 1971. They placed a 7-mm Teflon tube graft from the main pulmonary artery to the descending aorta. The technique was further reported in 1975 [16]. Zahka and co-workers [17] described the use of polytetrafluoroethylene tubes to restore aortic continuity through a left thoracotomy, either as a staged procedure or as part of a combined one-stage repair. This method has several advantages: it does not require full mobilization of the aorta, the sacrifice of any major vessel, or the use of any ductal tissue. One major drawback, however, is that as the infant grows, the graft will have to be replaced with a larger conduit, although early follow-up has shown no gradients across these conduits [18, 19]. It is inevitable that any conduit measuring between 4 and 10 mm will become restrictive and require replacement.

The subclavian and common carotid arteries or the duct itself have been used to achieve aortic continuity since the earliest attempts to palliate or correct this condition [20]. In a series of 12 patients presented by Monro and associates [10], direct repair was not thought possible in 5 patients. A combination of ductal tissue, subclavian flaps, or turned down carotid arteries was used. In a series of 17 patients, Fowler and colleagues [21] sacrificed the subclavian artery in 2 patients, one of whom died. In a large series [22] from Boston, MA, and Birmingham, AL, nearly 20% of the patients required the use of either the duct or the left subclavian artery to correct the defect, with a 40% mortality rate (the more recent experience suggests considerable improvement in these figures).

It would appear that two-stage palliative procedures can offer benefits over the one-stage correction. In a study of survival determinants in 26 patients, Quereshi and co-authors [8] found that a two-stage operation was associated with a significantly improved survival compared with a one-stage procedure. The operation to restore aortic continuity through a left thoracotomy was first performed in 1966. At that time, the mortality rate was 26%, and direct anastomosis was not considered possible. Since then, it has been described in a proportion of reported cases. In our series, we were able to perform direct anastomosis of the aorta in 10 of the 11 patients; in the remaining patient, in whom the ascending aorta was too small, the underside of the left common carotid artery was used. This patient was the only one to show a residual gradient. As aortic continuity had been restored, it was a straightforward procedure to augment the arch with a pericardial patch at the second operation.

Of the three deaths in our series, only one can be directly attributed to the two-stage procedure, that of the neonate who died of a pulmonary hypertensive crisis after the second operation. With this taken into account, the mortality rate attributable to the procedure in this series was 9%.

We believe that direct anastomosis is possible because of two factors. The first is full mobilization of the aorta from the level of the diaphragm to the apex of the pleural cavity. The second is the application of a proximal clamp to include a part of the innominate artery and ascending aorta, with the caveat that there must be an arterial pressure of at least 50 mm Hg in the right arm. This technique has allowed us to perform direct anastomosis without tension and without sacrificing any intercostal artery or jeopardizing cerebral function.

In conclusion, we advocate the use of echocardiography rather than angiography for the diagnosis of suspected arch interruption, and prostaglandin E infusion to maintain patency of the duct until operation. Furthermore, we suggest initial palliative operation through the left chest using end-to-end reconstruction to restore aortic continuity.

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Thromboelastogram Fails to Predict Postoperative Hemorrhage in Cardiac Patients

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To determine the clinical usefulness of the thromboelastogram in the prediction of postoperative hemorrhage in cardiac patients, we related the results of routine coagulation tests (RCTs) and thromboelastography with the amount of chest tube drainage postoperatively in 101 patients requiring cardiopulmonary bypass. Our data indicated that there was no correlation between RCT results and thromboelastographic variables. No single variable of RCTs and thromboelastography correlated well with the amount of chest tube drainage postoperatively. Before the onset of cardiopulmonary bypass, the most frequent abnormalities detected by thromboelastograms were fibrinolysis and hypocoagulability resulting from factor deficiency. Hypercoagulability detected by thromboelastograms occurred in 13% of patients after cardiopulmonary bypass and usually was not detected by RCTs. The incidence of false-negative thromboelastograms and RCT results in patients who had excessive hemorrhage of unknown cause was 46% and 52%, respectively. The incidence of fibrinolysis as detected by thromboelastograms was similar before and after bypass, but only 2 of the 18 patients with fibrinolysis had excessive hemorrhage postoperatively. Our results indicate that neither RCTs nor thromboelastography predicts the likelihood of excessive hemorrhage in patients after cardiopulmonary bypass. The thromboelastographic results should be interpreted cautiously because of the high rate of unreliable results.

(Ann Thorac Surg 1992;53:435–9)

Despite the improvements in cardiac surgery and in cardiopulmonary bypass (CPB) equipment, there are patients who experience severe and occasionally life-threatening hemorrhage after CPB. A high percentage of these patients require transfusion and sometimes reoperation. Hemorrhage occurs in 5% to 18% of patients who have undergone open heart procedures [1–4]. Many abnormalities, such as thrombocytopenia, fibrinolysis, factor deficits, inadequate neutralization of heparin sodium by protamine sulfate, and complement activation, can occur during and after CPB. Inadequate surgical hemostasis is also frequently cited as a cause of problematic hemorrhage after CPB.

The detection of these defects is often based on clinical evaluation and on the results of laboratory coagulation screening tests. The use of a standard screening battery consisting of platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen level, and fibrinogen degradation products has been suggested as a means of assessing causes of bleeding [5]. A potential problem facing the physician who manages bleeding patients is the long laboratory turnaround time. Rapid changes in the coagulation status of patients can occur, not only as a result of hemorrhage, but also as a result of transfusion. The delay in obtaining results of coagulation screening tests often diminishes their potential utility in guiding the therapy for these patients.

Although some interventions have been successful in reducing bleeding after CPB, excessive bleeding remains a major cause of morbidity and mortality, and it is sometimes difficult to manage such incidents with the currently available coagulation tests. Thromboelastography, a test of viscoelastic clot strength, has proved to be valuable in the detection of some specific abnormalities of hemostasis. Clinical studies [6–8] on the validity of thromboelastography-guided therapy have suggested that it may be useful in the operating room. Thromboelastographic (TEG) variables were correlated with fibrinogen level, activated clotting time, and activated partial thromboplastin time in patients undergoing CPB and those not having CPB [6, 7]. It has been suggested that thromboelastography provides a unique means of assessing platelet activity and fibrinolysis, two common causes of postoperative bleeding in cardiac surgical patients. We hypothesized that analyzing the thromboelastograms of patients after CPB would allow us to predict which patients will bleed and that thromboelastography would assist us in rapidly diagnosing and treating the underlying causes of bleeding after CPB in a way that routine coagulation tests (RCTs) could not.

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Material and Methods

After obtaining approval from the institutional review board, we studied 101 consenting patients undergoing coronary artery bypass grafting (CABG), valve replacement procedures, or both. All CABG patients were premedicated with morphine sulfate (0.1 mg/kg), scopolamine hydrobromide (0.4 mg), and sodium pentobarbital (1 mg/kg), or diazepam (10 mg). The dose of premedications was reduced by half in patients with valvular disease. Anesthesia was induced with high-dose fentanyl and muscle relaxants, supplemented with nitrous oxide and enflurane or isoflurane as necessary.

The extracorporeal circuit was primed with 1,700 mL of crystalloid solution, which contained 6,000 units of heparin. The perfusion flow rate at hypothermia of 25° to 27°C was 2.0 to 2.4 $L \cdot min^{-1} \cdot m^{-2}$ with use of a membrane oxygenator. Bovine lung heparin (200 to 300 U/kg) was given through a central intravenous injection before cannulation of the aorta. Activated clotting times were measured before cannulation, after heparin injection, at 1-hour intervals during CPB, and after protamine administration with a Hemochron 400 automatic timing device (International Technidyne Corp, Edison, NJ). Additional heparin was administered if the activated clotting time fell to less than 400 seconds. After patient rewarming and weaning from CPB, the residual heparin was neutralized with protamine sulfate (1 mg/100 U of previously administered heparin). The effect of protamine neutralization was verified by return of the activated clotting time to the normal range.

After the patient was transported to the surgical intensive care unit, routine respiratory and volume support was administered, and hemodynamic stability was achieved. Blood from the chest tube drain was reinfused into the patient through an autotransfusion device for the first 8 hours after operation. The amount of chest tube drainage was recorded at 1, 6, 12, and 24 hours postoperatively and was kept under observation until removal of the thoracotomy drainage tubes. Excessive bleeding was defined as chest tube drainage of more than 10 mL/kg for the first hour and more than 200 mL/h during the first 6 hours after operation.

Blood samples for routine laboratory coagulation tests, hematocrit measurement, and the TEG tracing were drawn from the radial arterial line after induction of anesthesia and again 10 minutes after protamine administration. The RCTs included activated clotting time, prothrombin time, activated partial thromboplastin time, and platelet count. Thromboelastography was performed on 0.35 mL of whole blood using a commercially available thromboelastograph (dual-channel biclot elvi 861 thromboelastograph; Logos Scientific Inc, Henderson, NV). The thromboelastograph was kept running for more than 60 minutes after the maximum amplitude appeared. The interpretation of the thromboelastogram in terms of R (reaction time), K (coagulation time), MA (maximum amplitude), and Ma 60 (amplitude 60 minutes after the MA) was identical to that used previously [6, 7]. Abnormalities of coagulation test results and TEG profiles were defined as values exceeding the normal range by 20%.

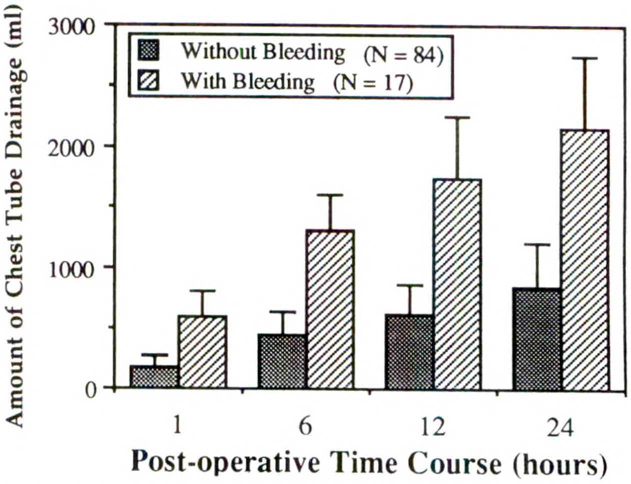

Fig 1. Comparison of the amount of chest tube drainage postoperatively in patients with and patients without excessive hemorrhage. The difference between the two groups was significant ($p < 0.001$) *at each time of recording.*

The relationship between the coagulation screening test variables, the hematocrit value, the TEG variables, and the amount of chest tube drainage was studied by means of multifactorial correlation analysis. We used the paired Student's t test to compare the data before and after CPB. The χ^2 test was used for analysis of the distribution of RCT and TEG variables in patients with excessive hemorrhage.

Results

Our study included 101 patients (72 male, 29 female) who underwent the following operations: CABG, 72; redo CABG, 7; mitral or aortic valve replacement, 12; and combined CABG and valve replacement, 10. Most of the CABG procedures included the internal mammary artery. The intraoperative course in all patients was uneventful. Of the 101 patients studied, 17 experienced excessive hemorrhage postoperatively, and of these, 5 patients required reexploration because of suspected surgical bleeding according to the widely accepted criteria [9]. Active bleeding was documented and stopped in 4 of these 5 patients, and only diffuse bleeding was noted in the fifth patient. The amount of postoperative chest tube drainage in patients both with and without excessive hemorrhage over time is illustrated in Figure 1. Two other patients died of low cardiac output syndrome postoperatively.

A comparison of the RCT and TEG variables before and after CPB is shown in Table 1. The R and K values in the TEG tracing were shortened significantly after CPB, whereas the MA and Ma 60 values did not change significantly. After CPB, the activated clotting time, hematocrit, and platelet count decreased, whereas the prothrombin time and activated partial thromboplastin time increased.

Table 1. Comparison of Thromboelastographic and Coagulation Test Variables Before and After Cardiopulmonary Bypass in 101 Patients

Variable	Before Bypass	After Bypass	p Value
Hematocrit	0.36 ± 0.06	0.23 ± 0.03	<0.001
Routine coagulation tests			
ACT (s)	156 ± 28.5	145 ± 22.8	<0.01
PT (s)	12.9 ± 1.04	14.4 ± 1.74	<0.001
aPTT (s)	28.7 ± 7.27	32.2 ± 8.38	<0.005
Platelets	295 ± 104.1	203 ± 97.5	<0.001
Thromboelastograms			
R (min)	14 ± 3.5	11 ± 4.3	<0.001
K (min)	4 ± 1.6	3 ± 2.6	<0.05
MA (mm)	55 ± 7.4	56 ± 8.2	NS
Ma 60 (mm)	46 ± 16.4	45 ± 17.8	NS

ACT = activated clotting time; aPTT = activated partial thromboplastin time; K = coagulation time; MA = maximum amplitude; Ma 60 = amplitude 60 minutes after MA; NS = not significant; PT = prothrombin time; R = reaction time.

Table 3. Coefficients of Correlation Between Amount of Chest Tube Drainage and Thromboelastographic and Coagulation Test Variables After Cardiopulmonary Bypass

Variable	Time After Arrival in Surgical ICU			
	1 Hour	6 Hours	12 Hours	24 Hours
Hematocrit	0.096	0.006	0.050	0.053
Routine coagulation tests				
ACT	0.107	0.027	0.025	0.011
PT	0.160	0.132	0.118	0.110
aPTT	0.058	0.057	0.121	0.175
Platelets	0.236	0.323	0.326	0.292
Thromboelastograms				
R	0.002	0.073	0.070	0.080
K	0.122	0.082	0.079	0.068
MA	0.281	0.248	0.276	0.275
Ma 60	0.074	0.035	0.007	0.005

ICU = intensive care unit; other abbreviations are the same as in Table 1.

Before CPB, there was no correlation between the TEG and RCT variables (Table 2). Also, none of the variables for either TEG or RCT correlated well with the amount of chest tube drainage postoperatively (Table 3). The incidence of abnormal RCT and TEG results in patients who did not experience excessive hemorrhage postoperatively was 41% and 43%, respectively. Among 13 patients who had excessive hemorrhage of unknown cause, the TEG tracing was normal in 46%, and 52% had normal RCT results (Table 4). None of the RCT or TEG abnormalities showed a significant difference between operation-related hemorrhage and hemorrhage of undefined cause.

Table 5 shows the distribution of abnormalities discovered from the TEG tracings in all patients. The most common abnormalities during the period before bypass included hypocoagulability due to factor deficiency and fibrinolysis. After CPB, major abnormalities were hypercoagulability and fibrinolysis. An abnormal thromboelastogram was found more often in CABG patients than in patients having valve replacement. Fibrinolysis occurred in similar numbers of patients both before and after CPB, but only 2 of the 18 patients with fibrinolysis experienced excessive hemorrhage after CPB.

Table 2. Coefficients of Correlation Between Thromboelastographic and Coagulation Test Variables in Patients Before Cardiopulmonary Bypass

RCTs	TEGs			
	R	K	MA	Ma 60
Hematocrit	0.075	0.174	0.400	0.160
ACT	0.168	0.223	0.004	0.117
PT	0.059	0.085	0.080	0.030
aPTT	0.011	0.109	0.077	0.017
Platelets	0.089	0.052	0.075	0.059

RCTs = routine coagulation tests; TEGs = thromboelastograms; other abbreviations are the same as in Table 1.

Comment

The multiple factors that contribute to postoperative hemorrhage in patients undergoing CPB complicate its diagnosis and treatment. Without a specific diagnosis from laboratory tests, the selection of treatment usually is based on a general understanding of the hemostatic abnormalities that occur in cardiac patients. Empirical therapy for these patients may put them at risk from both continued hemorrhage and infection from contaminated blood products.

Coagulation is a dynamic process in which many factors are involved. Routine coagulation tests provide limited information about the quality of clots because they identify only the first stage of clotting. In contrast, theoretically, thromboelastography measures the entire process of clotting from the time of initial fibrin formation to eventual clot lysis, and it should provide more information than do RCTs. However, in previous studies [10] on thromboelastography, a weak correlation between it and RCTs was reported in patients with hypocoagulability, whereas the correlation was higher in patients with hypercoagulability. Thromboelastography can identify platelet dysfunction as well as thrombocytopenia [11]. A greater predictive accuracy of the thromboelastogram compared with RCTs for postoperative bleeding in cardiac patients has been reported [7, 12]. In our daily practice, however, we often find that patients with hemorrhagic diathesis have normal TEG tracings and that abnormal TEG tracings can be encountered in patients without any clinical indication of a bleeding diathesis. Therefore, the

Table 4. Distribution of Coagulation Test and Thromboelastographic Variables in Patients With and Without Excessive Hemorrhage After Cardiopulmonary Bypass

	Patients Without Excessive Hemorrhage (n = 84)		Patients With Excessive Hemorrhage			
			Operation Related (n = 4)		Undefined (n = 13)	
Variable	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Routine coagulation tests						
ACT	68	16	4	0	12	1
PT	29	55	3	1	4	9
aPTT[a]	44	28	4	0	7	6
Platelets	51	33	3	1	4	9
Thromboelastograms	48	36	4	0	6	7

[a] Data were not obtained in 12 patients without excessive hemorrhage.

Abbreviations are the same as in Table 1.

validity of the thromboelastogram in predicting hemorrhage after CPB appears questionable.

Based on the previously established diagnostic standard for thromboelastography [11], our data indicate that, on the thromboelastogram, factor deficiency is much more common than are platelet-related abnormalities in patients before CPB. Fibrinolysis and hypercoagulability are the more common coagulopathies in our patients after CPB, but these two conditions do not predict the occurrence of excessive bleeding. There was no correlation between the amount of blood drained from the chest tube and the TEG and RCT variables. In patients having excessive hemorrhage of unknown cause, the incidence of normal results of RCTs after CPB was almost identical to that of the thromboelastograms.

The weak correlation between the RCT and TEG variables in patients before CPB has been attributed to the effects of medications on platelet function [7]. We were surprised to find from the TEG tracings that the major reason for hypocoagulability before CPB was factor deficiency, and that the incidence of platelet dysfunction before bypass in our patients was not as high as that in other reports [13]. This may be related to differences in the patterns of use of drugs that affect platelet function. Even though factor deficiency and fibrinolysis were indicated preoperatively by thromboelastograms, we were unable to identify the reason. The indicated high rate of occurrence of fibrinolysis and factor deficiency in our patients before bypass suggested that the high incidence of false-positive results of thromboelastography might contribute to its limited specificity. Forty-six percent of 13 patients with excessive hemorrhage of unknown cause after CPB had normal TEG tracings. In these patients, there was no specific reason for hemorrhage, and 12 of the 13 did not undergo reexploration. Thus, the false-negative rate of thromboelastography in these patients was 46%. The RCTs had almost the same frequency of false-negative results in these 13 patients (52%). The use of thromboelastography for rapid assessment of coagulation in this population of patients who underwent CPB was thus of limited value because of the high incidence of false-positive and false-negative results. We were unable to identify any specific TEG abnormality as predictive or causative of excessive bleeding after CPB.

Hypercoagulability could be detected in the TEG tracing after CPB but could not be specifically detected with RCTs. Before operation, none of our patients had accelerated coagulation. However, we detected hypercoagulability after CPB in 13% of the patients. A similar phenomenon has been observed and reported by other researchers

Table 5. Thromboelastographic Abnormalities in Patients Undergoing Cardiopulmonary Bypass[a]

	Before Bypass (n = 37)		After Bypass (n = 34)	
Abnormality	CABG	Valve Replacement	CABG	Valve Replacement
Hypocoagulability	19	7	9	2
Platelet abnormalities	2	3	2	1
Factor deficiency	17	4	7	1
Hypercoagulability	0	0	11	2
Fibrinolysis	16	2	16	2

[a] Multiple abnormalities occurred in several patients.

CABG = coronary artery bypass grafting.

[13], but without explanation. We did not specifically test the cause of the accelerated coagulation after CPB; however, some interventions during CPB may be responsible for this effect. First, the abnormal physiologic state created by the extracorporeal circuit produces a marked stress response [14]. A temporary increase in catecholamines in relation to the events during CPB has been observed in cardiac surgical patients. The precise cause or mechanism by which the coagulation system interacts with catecholamines is not clear; however, platelet aggregation is activated [15]. The addition of epinephrine accelerated blood coagulation in an animal model [16]. In research on the effect of blood loss on the thromboelastogram, patterns of accelerated coagulation in the TEG tracing have been reported, and the hypercoagulability that occurred during blood loss was ascribed to initiation of a stress response [17]. Accelerated coagulation as detected by thromboelastography occurs mainly in CABG patients. After such patients have been weaned from CPB, calcium is routinely used in our institution for enhancement of ventricular contraction. The action of calcium as a coagulation factor may explain the accelerated coagulation observed in these patients. In addition, CPB results in hemodilution, as detected by hematocrit measurement. It has been suggested that hematocrit correlates well with MA in the TEG tracing [18]. However, a poor correlation between hematocrit and TEG variables in our study suggests that hypercoagulability in the TEG tracing did not consistently result from a decrease in hematocrit. The mechanism of accelerated coagulation in the thromboelastogram needs further investigation.

The detection of hypercoagulability in the thromboelastogram suggests that the thromboelastogram may provide more information than do RCTs about the coagulation process. In addition, the pattern of accelerated coagulation may offset other abnormalities induced by CPB, such as factor deficiency. The limited value of the thromboelastogram in predicting postoperative hemorrhage may result from the presence of hypercoagulability after CPB. However, no patient with excessive bleeding after CPB demonstrated accelerated coagulation in the TEG tracing. An association of hypercoagulability with a low predictive value of the thromboelastogram seems unlikely based on the results for our patients.

Our data suggest that neither RCTs nor TEG monitoring of coagulation provides timely predictive information about the presence or absence of excessive hemorrhage after CPB. The high percentage of false-negative and false-positive results of the TEG tracing limits its value as a reliable predictor of postoperative bleeding. Even though the presence of hypercoagulability in the thromboelastogram indicates that the tracing may contain more information on blood coagulation than do RCTs, the results should be interpreted with caution because of the high rate of unreliable results.

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Cardiac Function and Myocardial Performance of 24-Hour–Preserved Asphyxiated Canine Hearts

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A method of 24-hour storage of asphyxiated canine hearts for orthotopic cardiac transplantation was studied to expand the geographical size of the donor pool. Left ventricular function of asphyxiated hearts preserved for 24 hours (group 1, n = 8) was compared with that of hearts donated on-site (group 2, n = 5). Group 1 donors were pretreated with verapamil hydrochloride, propranolol hydrochloride, and prostacyclin. The donor hearts were perfused with warm blood cardioplegia in situ after 10 minutes of asphyxiation and then perfused with cold crystalloid cardioplegia for 2 hours. The hearts were excised and stored in ice-cold University of Wisconsin solution for 22 hours. At orthotopic transplantation, coronary perfusion with warm blood cardioplegia was performed before the graft aorta was unclamped. Conventional cardiac variables (eg, cardiac output and maximum rate of rise of left ventricular pressure), myocardial performance, and diastolic compliance of grafted hearts were assessed 1 hour after weaning from bypass. All recipients in both groups were easily weaned from cardiopulmonary bypass without inotropic agents, and there were no significant differences in cardiac variables between the two groups. These results strongly suggest that cadaver hearts can be preserved for 24 hours with satisfactory cardiac function.

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Although orthotopic heart transplantation has had satisfactory results worldwide, ventricular failure is the leading cause of death during the first 30 postoperative days [1]. The cause of early graft failure appears to be a prolonged period of ischemia and inadequate preservation. From 1980 to 1986, the number of heart transplantations increased exponentially, but the rate of increase subsequently slowed [1]. This slowing may reflect the shortage of available donors. Because of these factors, greater attention needs to be directed to prolonging the preservation period by an easy and safe method. Furthermore, it seems valuable to develop a preservation method for hearts harvested after cardiac death or situations where a major warm ischemic myocardial insult is unavoidable.

Previously, we [2–4] have investigated the possibility of myocardial resuscitation and preservation of asphyxiated hearts. In the present study, we evaluated the intrinsic myocardial performance and diastolic compliance in addition to conventional indices of left ventricular (LV) function of asphyxiated canine hearts stored for 24 hours as a model of the donor heart injured by warm ischemia.

Material and Methods

Animals

Twenty-six mongrel dogs weighing 5.2 to 19.7 kg (average weight, 12.5 ± 3.6 kg) were used for orthotopic heart transplantation. Of the 13 donor hearts, 8 were asphyxiated for 10 minutes and preserved for 24 hours (group 1). The other 5 were excised and preserved by the same method as used in clinical transplantation (group 2). All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Method of Preserving Donor Hearts

The experimental protocol for the preservation of group 1 donor hearts has been described previously (Table 1) [3, 4]. In brief, donor dogs were anesthetized, intubated, and ventilated. A left thoracotomy was performed initially to determine baseline cardiac function. A catheter was placed in the ascending aorta through the brachiocephalic trunk to perfuse the coronary vessels selectively with aortic arch occlusion. A 10F polyethylene drainage tube was introduced into the right atrium through the femoral vein to evacuate the perfusate.

Dogs were exsanguinated to induce antemortem shock, during which the systolic aortic pressure was kept lower than 50 mm Hg for at least 20 minutes. During this hypotensive period, the donor was pretreated with an infusion of prostacyclin analogue (PGI_2A) (15-cyclopentyl-w-pentanol-5(E)-6,9 metanoprostacyclin) (0.02 mg/kg), verapamil hydrochloride (0.5 mg/kg), and propranolol

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Table 1. *Method of Preserving Donor Hearts*

Step	Process Time
Exsanguination, pretreatment	20 min of antemortem hypotension
Respirator off	10 min of asphyxia
In situ coronary perfusion with warm blood cardioplegia	5 min
Washout of coronary vascular bed and in situ coronary perfusion with cold cardioplegia	2 h (held at 15°–17°C)
Removal and immersion in University of Wisconsin solution (4°C)	22 h
Orthotopic heart transplantation	45 min
Coronary perfusion with warm blood cardioplegia	10 min
Aortic unclamping, heart kept nonworking and beating	30 min
Weaning from cardiopulmonary bypass and observation	1 h
Measurement of cardiac function	

hydrochloride (0.5 mg/kg). Apnea was induced by the injection of pancuronium bromide (0.08 mg/kg) and by stopping respiratory support. Cardiac arrest occurred in all animals within 10 minutes of asphyxia [4].

After 10 minutes of asphyxia, coronary vessels were perfused with 10 mL/kg of hyperkalemic blood cardioplegia [5] at room temperature through the catheter in the aortic root. After warm blood cardioplegia (WBCP) perfusion, the coronary vascular bed was washed out with 10 mL/kg of ice-cold crystalloid cardioplegia containing PGI_2A (0.6 mg/L) and verapamil (0.5 mg/L) and perfused continuously with that solution at a flow rate of 0.5 to 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ to maintain the myocardial temperature between 15° and 17°C for 2 hours. The compositions of the two cardioplegic solutions are shown in Table 2.

The in situ preserved heart was excised and immersed in ice-cold University of Wisconsin (UW) solution containing PGI_2A (0.6 mg/L) and verapamil (0.5 mg/L) for 22 hours. Before immersion in cold UW solution, the excised heart was flushed with 10 mL/kg of the storage solution. The heart was stored for 24 hours and then transplanted orthotopically under cardiopulmonary bypass. Coronary perfusion with WBCP was carried out again just before the graft aorta was unclamped.

The hearts arrested by cold cardioplegia in group 2 were excised and immersed in ice-cold modified Collins solution for 3 hours.

Table 2. *Composition of Cardioplegic Solutions*

Component	Blood Cardioplegia	Crystalloid Cardioplegia
5% glucose solution (mL)	200	500
50% glucose solution (mL)	0	30
1 mol/L potassium chloride (mL)	15	10
7% sodium bicarbonate (mL)	15	15
Heparin (1,000 U/mL) (mL)	1	1
Insulin (U)	0	8
Arterial blood (mL)	300	0

Transplantation Procedure

The recipient dogs were prepared as already described. A left thoracotomy was performed in the fourth intercostal space. The preserved hearts were transplanted according to the method of Lower and Shumway [6]. All recipients were weaned from bypass without inotropic support using cardiac pacing at a fixed rate of 120 beats per minute.

Hemodynamic Assessment

One hour after bypass, conventional variables of cardiac function (LV pressure, maximum rate of rise of LV pressure, maximum negative rate of rise of LV pressure, cardiac output), myocardial performance (preload recruitable stroke work [PRSW]), and diastolic compliance of the grafted hearts in groups 1 and 2 were measured and compared. These indices also were compared with preharvest baseline levels in each group.

Data acquisition and analysis of the PRSW [7] were performed as follows: A 5F micromanometer (model MPC-500; Millar Instruments, Houston, TX) and an 8F conductance catheter (Cordis Europa NV, Roden, the Netherlands) were inserted into the left ventricle through the apex. The instantaneous LV pressure was measured by the micromanometer, and the instantaneous LV volume was measured by the conductance catheter and a volumetric system (Sigma 5; Leycom, Ocgstgeet, the Netherlands). The LV pressure and LV volume data were transmitted simultaneously to a signal processor (San-Ei 7T184; Sanei Inc, Tokyo, Japan) using software (developed by Taisho Biomedical Institute, Osaka, Japan) that permitted real-time inspection of the LV pressure–volume loops. Linear regression analysis of the dynamic LV pressure–volume relationship during transient acute volume unloading induced by 10 seconds of occlusion of the inferior vena cava allowed measurement of the stroke work (SW)–end-diastolic volume (EDV) relationship. The pooled data scatter plot was fitted to the formula $SW = M(EDV - V_0)$, in which the slope (M) was defined as the PRSW. Diastolic compliance was assessed from the linear relationship between end-diastolic pressure (LVEDP) and LVEDV (EDP/EDV) obtained from the pressure–volume loops during transient acute volume unloading.

Statistical Analysis

Data are expressed as the mean ± the standard deviation. Significance was tested using either Student's unpaired or paired *t* test as appropriate, taking a *p* value of 0.05 as the limit of significance.

Table 3. Cardiac Function and Myocardial Performance of Grafted Hearts Before Harvesting Versus After Transplantation

Time	LV Pressure (mm Hg)	dP/dt max (mm Hg/sec)	−dP/dt max (mm Hg/sec)	Cardiac Output (mL · kg^{-1} · min^{-1})	PRSW ($\times 10^3$ erg/mL)	EDP/EDV (mm Hg/mL)
Group 1						
Before harvesting	141 ± 26	2,429 ± 472	1,714 ± 455	129 ± 29	92.6 ± 22.1	0.281 ± 0.029
After transplantation	111 ± 18	1,713 ± 300	1,275 ± 268	128 ± 28	101.7 ± 19.1	0.270 ± 0.030
p Value (before versus after)	NS[a]	<0.02[a]	NS[a]	NS[a]	NS[b]	NS[b]
Group 2						
Before harvesting	138 ± 22	2,194 ± 289	1,828 ± 205	ND	85.5 ± 21.0	0.295 ± 0.042
After transplantation	121 ± 16	2,044 ± 329	1,695 ± 203	122 ± 10	91.2 ± 13.5	0.318 ± 0.059
p Values (before versus after)	NS[a]	NS[a]	NS[a]	. . .	NS[b]	NS[b]
p Values						
p Group 1 versus 2, before	NS[a]	NS[a]	NS[a]	. . .	NS[a]	NS[a]
p Group 1 versus 2, after	NS[a]	NS[a]	NS[a]	NS[a]	NS[a]	NS[a]

[a] Significance by unpaired *t* test. [b] Significance by paired *t* test.

dP/dt_{max} = maximum rate of rise of left ventricular pressure; $-dP/dt_{max}$ = negative maximum rate of rise of left ventricular pressure; EDP = end-diastolic pressure; EDV = end-diastolic volume; LV = left ventricular; ND = not done; NS = not significant; PRSW = preload recruitable stroke work.

Results

All recipients were easily weaned from cardiopulmonary bypass without the use of any catecholamines. Hemodynamic function remained stable without inotropic support during the 1-hour observation period after bypass. Left ventricular end-diastolic pressure was held at approximately 5 mm Hg by controlling the circulatory blood volume during the observation period. The LV systolic pressure of the recipients was not significantly different from the preharvest baseline value (Table 3). The maximum rate of rise of LV pressure measured after transplantation was not significantly different between groups 1 and 2 but was significantly lower than baseline in group 1 ($p < 0.02$). For the maximum negative rate of rise of LV pressure, there was no significant difference between groups or between preharvest and posttransplantation values.

The mean cardiac output after transplantation in group 1 (128 ± 28 mL · kg^{-1} · min^{-1}) and group 2 (122 ± 10 mL · kg^{-1} · min^{-1}) were not different from baseline (129 ± 29 mL · kg^{-1} · min^{-1}). The mean PRSW 1 hour after transplantation was $101.7 \pm 19.1 \times 10^3$ erg/mL in group 1 and $91.2 \pm 13.5 \times 10^3$ erg/mL in group 2. The PRSW of the grafted hearts after transplantation was not significantly different from the preharvest baseline. The EDP/EDV 1 hour after transplantation was similar in groups 1 and 2 and there was no significant difference from baseline in either group (see Table 3).

Comment

In the late 1960s, intensive experimental studies involving cadaver hearts were performed, and some successful orthotopic heart transplantations were reported [8–10]. However, the methodology was inappropriate for clinical use and was abandoned. Further studies using cadaver hearts have been virtually suspended since 1972.

The myocardium of agonally arrested hearts is damaged by hypoxia during antemortem shock [11], anoxia during asphyxia [10], and warm ischemia from the moment of cardiac arrest until the start of preservation [8, 10, 12, 13]. We [2–4] have designed a broad series of experimental studies to establish the optimum method to resuscitate and preserve agonally arrested cadaver hearts for orthotopic transplantation. In this model, canine hearts were exposed to 20 minutes or more of hypotension to imitate antemortem shock and to 10 minutes of asphyxia to cause cardiac arrest and warm ischemia. Exsanguination was carried out to induce hypotension and to obtain autologous arterial blood for blood cardioplegia. In this situation, hypovolemia might have a role in preventing excessive cardiac distention. Although cardiac arrest occurs as a result of various causes in the clinical situation, asphyxia should be the most deleterious cause with respect to myocardial ischemic injury. That was the reason asphyxiation was used in this model.

To protect the myocardium against agonal asphyxia and warm ischemia until selective coronary perfusion was started, donor animals were pretreated with PGI$_2$A, verapamil, and propranolol. A high dose of propranolol was used to minimize the myocardial injury caused by high intrinsic epinephrine levels as a result of asphyxiation. Verapamil was used as an antiarrhythmic, vasodilating, and myoprotective agent. Prostacyclin is known to have vasodilating and antiplatelet actions and a cytoprotective effect [14].

We [3, 4, 15] have shown that selective coronary perfusion with WBCP after asphyxiation can restore damaged myocardium and that the intraoperative use of WBCP reduces postischemic reperfusion injury when combined with PGI_2A, verapamil, and propranolol. The concept of using initial perfusion with WBCP to rescue myocardium from ischemic injury was a modification of the controlled reperfusion described by Buckberg and colleagues [16–18]. To minimize reperfusion injury in the graft, coronary perfusion with WBCP was performed immediately before aortic unclamping, an idea that came from secondary blood cardioplegia [19–21]. Continuous coronary perfusion with cold crystalloid cardioplegia is considered inferior to single-dose cardioplegia followed by repeated intermittent perfusion in open heart procedures.

Although a left thoracotomy was done initially to determine preharvest cardiac function in this study, in the clinical situation, the asphyxiated heart should be stabilized and preserved in situ for several hours before thoracotomy. The donor heart cannot be cooled by topical cooling in the absence of pericardiotomy and is warmed by the surrounding tissue during the intervals between intermittent-dose cardioplegia. Therefore, the continuous coronary perfusion technique to maintain myocardial temperature at less than 20°C was essential for using a cadaver heart as the donor organ [3, 4].

The efficacy of UW solution was compared with modified Collins solution in the 24-hour–storage system [4]. Cardiac output and ultrastructural findings suggested that UW solution is better than modified Collins solution as a storage solution in this system.

In this study, we evaluated conventional cardiac variables, intrinsic myocardial performance, and diastolic compliance of asphyxiated canine hearts stored for 24 hours and then placed orthotopically. As the conventional indices of LV function, such as cardiac output and maximum rate of rise of LV pressure, are known to be load-dependent, true cardiac function or intrinsic myocardial performance of the grafted hearts in recipients cannot be compared with those in donors. Therefore, we introduced the PRSW as myocardial performance and LVEDP/LVEDV as diastolic compliance to assess the LV function of the grafted heart after transplantation. These variables were developed as alternative indices that incorporate whole cardiac cycle events into the assessment of myocardial performance [22–24] and diastolic function.

All animals that received 24-hour–preserved asphyxiated cadaver hearts were weaned from cardiopulmonary bypass without inotropic support. Not only the conventional cardiac variables but also the intrinsic myocardial contractility and the diastolic compliance of the grafted hearts revealed that the cadaver hearts could function as satisfactorily as hearts donated on-site. The PRSW and the EDP/EDV of the grafted hearts also indicated that there was no significant difference in LV function between preharvest baseline and posttransplantation values.

In conclusion, our results indicate that a cadaver heart can be preserved for at least 24 hours using blood cardioplegia for prevention of both warm and cold ischemic damage and UW solution as the storage solution in combination with PGI_2A, verapamil, and propranolol as myoprotective drugs.

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Preoperative Chemotherapy and Radiation Therapy for Stage IIIa Carcinoma of the Lung

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Thirty-six patients with stage IIIa histologically proven non–small cell carcinoma (T3 N2 or T2 N2) underwent concomitant radiation therapy and chemotherapy before pulmonary resection. The therapy consisted of two cycles of continuous infusion of *cis*-platinum, 25 $\mathrm{mg \cdot m^{-2} \cdot day^{-1}}$ (days 1 through 4) every 4 weeks and concomitant irradiation, 55 Gy, of the tumor and mediastinum. Two to 3 weeks after treatment, the patients were reevaluated for thoracotomy and pulmonary resection. Five patients were found to have unresectable lesions. Thirty-one patients had complete resection, 27 by radical pneumonectomy and 4 by radical lobectomy, giving a resectability rate of 86%. Complete sterilization of lung tumor and mediastinal nodes proven histologically was achieved in 10 patients (28%) and 17 patients (47%). The 3-year survival rate is 61.7% for patients who had resection. Median follow-up is 27 months (range, 6 to 61 months). The preliminary study indicates that preoperative *cis*-platinum and concomitant radiation therapy is tolerated, appears to increase resectability, and may improve survival in patients with stage IIIa lung cancer.

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Pulmonary resection remains the only accepted mode of therapy and hope for potential cure for patients with non–small cell lung cancer. Patients with stage I and stage II disease have a high rate of resectability, with an excellent chance for cure. However, the prognosis for patients with stage III locally advanced lung cancer with extension beyond the lung parenchyma treated surgically is rather poor, with a resectability rate of only 14% to 20% and a 5-year survival rate ranging from 9% to 34% [1, 2].

In our earlier study [3], none of our patients with histologically positive mediastinal nodes in the upper mediastinum who had radical pneumonectomy were alive at the end of 5 years. Although local control was achieved in the majority of these patients, distant relapse was a common cause of failure and death.

The addition of preoperative and adjuvant chemotherapy with or without irradiation has been shown to enhance resectability and perhaps prolong survival [4–6]. An induction regimen of *cis*-platinum–based chemotherapy and radiation therapy [7, 8] or *cis*-platinum–based chemotherapy alone [9, 10] has been associated with a resectability rate of 75%. Beginning in 1985, a pilot study was undertaken to treat patients with stage IIIa non–small cell lung cancer with concomitant chemotherapy and radiation therapy in the hope of improving resectability and ultimate survival.

Material and Methods

Thirty-six consecutive patients with a proven diagnosis of non–small cell bronchogenic carcinoma and positive mediastinal nodes (stage IIIa) were selected for the study. There were 26 men and 10 women with a median age of 58.3 years (range, 41 to 77 years). Ten patients had squamous cell carcinoma, 19 had large cell carcinoma, and 7 had adenocarcinoma. There were 19 T3 and 17 T2 lesions. All patients had metastasis to mediastinal nodes. Eight patients had bulky mediastinal nodes on plain chest roentgenograms. Tissue diagnosis of N2 involvement was made preoperatively in 34 patients. In the other 2 patients, the preoperative chest roentgenogram was consistent with bulky mediastinal metastasis. The patients had a complete evaluation, including history and physical examination. Patients with poor pulmonary function test results, superior vena caval obstruction, superior sulcus tumor, metastatic pleural effusion, contralateral or supraclavicular node involvement, or distant metastasis and poor-risk patients were excluded from the study. A complete metastatic workup to exclude any evidence of extrathoracic involvement was performed and included computed tomography of the chest and upper abdomen, pulmonary function tests, bronchoscopy, and mediastinoscopy or anterior mediastinotomy. Brain computed tomography was done in patients with any neurological symptoms. Bone scan was performed only in patients with bone pain. A creatinine clearance of 50 mL/min or greater was required for inclusion in the study.

Induction chemotherapy consisted of *cis*-platinum, 25 $\mathrm{mg \cdot m^{-2} \cdot day^{-1}}$ for 4 days (days 1 through 4) intravenously by continuous infusion with 3 L of normal saline

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solution daily, and VP-16 (etoposide), 100 mg/m^2 intravenously by infusion over 30 minutes on days 2 and 4. A second cycle of chemotherapy was initiated on day 28.

Beginning on day 1, concurrent radiation therapy was administered over the entire mediastinum from the suprasternal notch to the diaphragm. The contralateral hilum and supraclavicular area were not included in the field. The total radiation dose was 55 Gy in 28 sessions. An additional 540 cGY in three sessions was given to the tumor alone.

Two or 3 weeks after completion of the last day of therapy, the patient was reevaluated. The reevaluation included history, physical examination, chest roentgenography, and computed tomography of the chest and upper abdomen. Pulmonary resection was scheduled 4 to 6 weeks after the last day of treatment. Bronchoscopy was performed routinely. Anterior mediastinotomy, either on the right side or on the left side, was done if the computed tomographic study of the chest suggested the disease was technically unresectable.

Anesthesia management included insertion of a double-lumen endotracheal tube. Radical pulmonary resection (with complete resection of all gross tumor and mediastinal fat pad) by lobectomy or pneumonectomy was performed. To ensure total excision (ie, no viable tumor left behind), multiple biopsy samples were taken from the tumor area around the aortic arch and esophagus if there was any extension to these two structures. Dissection of the mediastinal fat pad started at the apex of the chest and was carried all the way down to the level of the hilum. In some patients, because of extension of the tumor to the mediastinum, the phrenic nerve and vagus nerve had to be sacrificed. In patients with a left-sided lesion, an attempt was made to preserve the recurrent laryngeal nerve in most cases. For better access to the hilar structures, the pericardium was opened, and pulmonary veins and arteries within the pericardium were ligated. The bronchial division was accomplished with a TA stapler, reinforced with interrupted 3-0 Prolene suture (Ethicon, Somerville, NJ), and covered by the pleura.

Three weeks postoperatively, the patient received an additional dose of *cis*-platinum, 25 mg $\cdot$ m^{-2} $\cdot$ day^{-1} intravenously for 5 days, and VP-16, 100 mg/m^2, intravenously. Two cycles of adjuvant chemotherapy were given at 28-day intervals.

Results

Five patients were found to have unresectable lesions because of extension to the esophagus, aorta, vena cava, trachea, and a second pulmonary lesion (one of each). Thirty-one patients underwent resection, a resectability rate of 86%.

Gross and Pathological Findings

In 5 patients, no definite gross tumor or demonstrable lymph nodes were identified at the time of thoracotomy. In the others, gross fibrosis of the mediastinum with remnants of adenopathy was noted. Shrinkage of tumor was seen in 6 patients. Twenty-three patients had a tumor larger than 5 cm; in the others, the tumor was less than 5 cm. In most patients with a large peripheral lesion, the tumor was found attached to the chest wall. Because of the size and extent of the lesion, 27 patients required radical pneumonectomy, and only 4 patients had lobectomy. In 3 patients, multiple-rib resection was done in addition to pulmonary resection.

Table 1. Pathological Findings of Resected Specimens[a]

Finding	Mediastinum (No. of patients)	Lung (No. of patients)
Viable abnormal cells of carcinoma	19 (53)	26 (72)
Necrotic tissue with no viable cells	17 (47)	10 (28)

[a] Numbers in parentheses are percentages.

Complete sterilization of the lung tumor and mediastinal nodes proven histologically was achieved in 10 patients (28%) and 17 patients (47%), respectively (Table 1). In 10 patients, no viable tumor cells were found in either lung or mediastinal nodes. In the rest, viable but altered cells of carcinoma were noted in the operative specimen. It was of interest that in 4 patients with a large tumor mass resected at operation, no viable cancer cells were noted. Necrotic tissue, mainly foreign-body giant cells forming macrophages and crystal clefts, was an integral part of this process.

There were two operative deaths (5.6%). Six patients required prolonged intubation and had radiological findings of acute respiratory distress syndrome. A bronchopleural fistula developed in 3 patients, early in 1 and late in 2. They were treated appropriately, either by conservative measures or by thoracoplasty.

Follow-up

Twelve patients have been followed up for more than 3 years. The 3-year survival rate was 61.7% for the patients who had resection. The median follow-up of these patients is 27 months (range, 6 to 61 months) (Fig 1).

Eight of the 10 patients with histologically negative resected specimens in the lung and mediastinum are alive and free from disease at 5 to 60 months postoperatively. Local control was achieved in 9 of these patients, and 2 patients had development of brain metastasis 2 years after resection.

Among the 31 patients who had pulmonary resection, only 1 patient had local recurrence. The principal sites of relapse included brain, bone, and contralateral lung.

Of the 5 patients who did not undergo resection because of local extension, 1 died at 6 months, 2 have recurrence but remain alive at 10 and 25 months, and 2 are free from disease at 12 and 34 months.

Comment

The role of neoadjuvant therapy in the management of stage III lung cancer is not yet defined. A number of

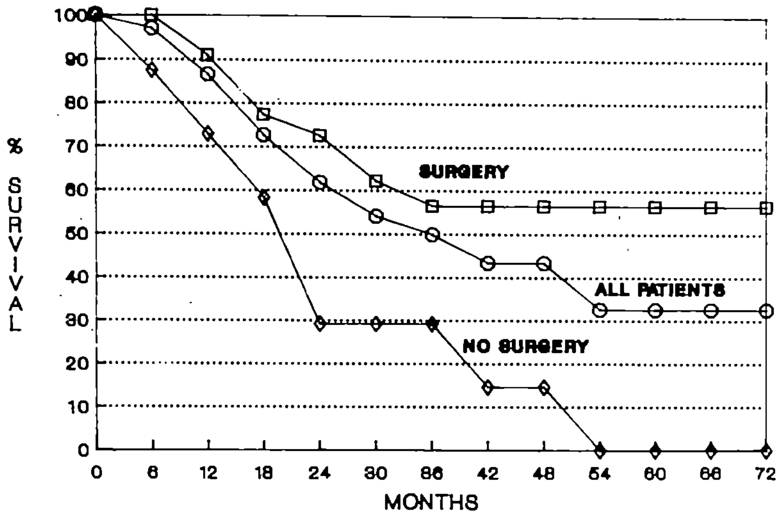

Fig 1. Survival of patients who underwent aggressive combined treatment program preoperatively for stage IIIa non–small cell carcinoma of lung.

critical studies [11–13] have been done to assess the value of preoperative chemotherapy alone or combined with irradiation in the management of patients with unresectable lesions of locally advanced carcinoma with mediastinal node involvement (N2). In a study at Memorial Sloan-Kettering Cancer Center [14], 30 of 41 patients showed a major radiographic response to a combination of *cis*-platinum with vindesine or vinblastine sulfate with or without mitomycin-C. After chemotherapy, 28 of these 30 patients underwent surgical treatment, with complete resection in 21 (75%) and total sterilization of the tumor proved histologically in 8. The 3-year survival rate was 34% for all patients. Taylor and colleagues [4] attained a 50% resectability rate in patients with simultaneous *cis*-platinum/fluorouracil infusion and irradiation followed by surgical resection. Twenty-three percent of patients surgically treated had histologically negative specimens after the preoperative treatment. In another trial by Strauss and co-workers [15] in which adjuvant chemotherapy was administered, the final resectability rate was 57%. Similar results were also described by Sridhara and associates [9].

Summarizing these experiences, it appears that with additional neoadjuvant chemotherapy, with or without irradiation, slightly more than 50% resectability could be obtained in patients with stage III non–small cell carcinoma with N2 involvement compared with 9% to 20% in patients without the benefit of preoperative neoadjuvant therapy [1,3,6]. Our 86% resectability rate appears to be higher than that reported in the literature and appears to be encouraging.

The result of local tumor control is also encouraging. Martini and co-workers [14] reported no residual tumor in the lung or mediastinal nodes in 29% and 14% of resected specimens, respectively. Taylor and associates [4] found that 23% of patients who underwent surgical resection had histologically negative specimens and that 21% had microscopic residual tumor only. In a similar study, Sridhara and colleagues [9] reported that complete sterilization of the resected specimen was achieved in 21%. In the present study, complete sterilization of the lung tumor and mediastinal nodes proven histologically was achieved in 28% and 47%, respectively.

A variety of combined therapies are now being used in several centers to assess the efficacy and benefit of preoperative chemotherapy or combined chemotherapy and radiation therapy in an attempt to improve the resectability and survival rates. Although the comparison of these studies is difficult because of variation in patient characteristics and methods of therapy [10, 16, 17], it appears that the best results are achieved in patients who undergo surgical resection of the lung and mediastinal lymph nodes.

In a trial conducted by the Lung Cancer Study Group [11], *cis*-platinum, 5-fluorouracil, and concurrent radiation therapy resulted in a response rate of 57% and a resectability rate of 80%. Complete sterilization of the tumor was achieved histologically in 23%, with a median survival of 10.5 months.

The resectability rate and the tumor control rate appear to be increased by concurrent chemotherapy and irradiation. Our resectability rate of 86% appeared to be higher than that shown in the literature, and a pathological complete response rate of 28% in the lung and 47% in the mediastinal nodes is most encouraging. The patients with complete tumor response appear to have excellent local control and a far better prognosis than those who have viable cancer cells in the resected specimen. Gralla and co-workers [12,17], using a combination of mitomycin and *cis*-platinum, found 25% of resected specimens were free of tumor, and 1-year and 2-year survival rates of 68% and 31%, respectively, were achieved. Holmes [20] reported that patients with a negative histological specimen had a survival advantage. Although a comparison of these studies is difficult because of variation in patient characteristics, doses, and mode of therapy, it appears that patients who achieve a complete pathological tumor response and have no viable tumor cells in the resected specimen have a survival advantage.

The toxicity of nonadjuvant chemotherapy is generally acceptable. The myelosuppression in our patients appeared to be mild. Gastrointestinal toxicity in the form of nausea and vomiting was seen in some patients. Taylor [4], Kaplan [8], Martini [14], and their colleagues have reported similar findings, including myelosuppression, nausea, vomiting, leukocytosis, and renal dysfunction.

The importance of performing operation no later than 4 to 6 weeks after induction of therapy cannot be overemphasized. Beyond this time frame, resection becomes very difficult because of fibrosis around the mediastinal structures.

In analyzing our results, it appears that the patients have benefited primarily by conversion of the tumor to a resectable state. Radiation therapy and chemotherapy per se achieved a minimal chance of survival (about 9 to 12 months) for these patients, as has been shown by many other studies.

When the sites of recurrence were analyzed in patients who underwent complete surgical resection, only 1 patient had local recurrence. Distant relapse is the usual finding in patients with stage IIIa disease, and of 7 patients with distant metastasis, 6 evidenced distal recurrence only. There were 2 patients with recurrence to the brain, 1 of whom had associated local recurrence.

Surgical complications after preoperative therapy were severe but tolerated. The incidence of bronchopleural fistulas in this group (3 patients) appears to be higher than that in patients undergoing pulmonary resection alone. This higher incidence is most likely related to a combination of preoperative irradiation and chemotherapy, and subsequent chemotherapy.

With the long follow-up, our 3-year survival rate of 61.7% for patients who had resection is higher than that reported in most published studies. Martini and associates [14] reported a 3-year survival of 54% for patients who had complete resection, and Strauss and co-workers [15], a 3-year survival of only 29%. The estimated 18 months' survival in the study by Taylor and co-authors [4] was 41%.

Our results indicate that preoperative treatment with *cis*-platinum and concomitant radiation therapy is well tolerated in patients with stage IIIa non–small cell lung carcinoma and appears to increase resectability and improve the survival rate in these patients.

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Intrapleural Bupivacaine in the Control of Postthoracotomy Pain

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A randomized, double-blind trial was conducted to determine the effectiveness of intrapleural bupivacaine hydrochloride in the management of pain after thoracotomy. Thirty-three men and 7 women with a mean age of 62 years (range, 21 to 76 years) undergoing elective posterolateral thoracotomy were randomly allocated preoperatively to either a study group receiving 20 mL of 0.25% bupivacaine or a control group receiving 20 mL of 0.9% saline solution through a pleural catheter every 4 hours. Patients received supplementary doses of intramuscular papaveretum as required. Assessment of pain, somnolence, and breathing capacity was performed after the intrapleural injections at 4, 24, 48, and 72 hours postoperatively. Pain assessment, as measured by a linear analog scale, was lower in the bupivacaine group at all times, reaching significance at 4, 24, and 72 hours ($p <$ 0.05). The forced vital capacity and forced expiratory volume in 1 second at 6 weeks postoperatively remained significantly lower than preoperatively ($p < 0.05$). The fall in forced vital capacity from this postoperative level was significantly less in the bupivacaine group at 4, 24, and 48 hours, and the fall in forced expiratory volume in 1 second was significantly less at 4 and 48 hours in the treated group. When used in conjunction with doses of parenteral narcotic, intrapleural bupivacaine gives better pain control with less respiratory depression than intermittent doses of narcotic alone.

(Ann Thorac Surg 1992;53:449–54)

Since the initial description by Reiestad and Strømskag [1], in 1986 the use of intrapleural anesthetic medication in the control of postoperative pain has become increasingly widespread. The effectiveness of this technique in upper abdominal surgery is well documented [1–6]. More controversial is the degree of analgesia provided by this method in patients after a posterolateral thoracotomy [2, 7–11].

At Repatriation General Hospital, Concord, Australia, we commenced using intrapleural injections of 0.25% bupivacaine hydrochloride in patients after posterolateral thoracotomy. The narcotic requirements of 8 patients receiving intrapleural bupivacaine were retrospectively compared with those of 8 patients receiving intramuscular narcotics alone. A 50% reduction in both the total dose and the number of doses of papaveretum over 72 hours was found in the group receiving bupivacaine. On the basis of this observation and in the absence in the literature of adequate randomized, double-blind studies, the following prospective randomized, double-blind trial was undertaken.

Material and Methods

With the approval of the hospital ethics committee, 40 patients undergoing elective posterolateral thoracotomy were entered into the study. Written informed consent was obtained from each patient preoperatively. Patients were excluded from entry into the trial if they underwent pneumonectomy or esophagectomy or had any contraindications to the administration of papaveretum or bupivacaine.

In all patients, a posterolateral thoracotomy was performed in the fifth intercostal space by or under the supervision of one of us (B.C.M.). Before closure of the thoracotomy, a clear nylon epidural catheter was inserted into the pleural space through a small incision above the thoracotomy using a Tuohy needle and positioned, under direct vision, to lie in the paravertebral gutter. The catheter was sutured to the skin. As is our usual practice, 36F intercostal catheters were placed anteriorly and posteriorly, and the thorax was closed in layers. The two intercostal catheters were connected by an underwater-seal drain to 20 cm H_2O suction.

Identical vials of 20 mL of 0.25% bupivacaine and 20 mL of 0.9% saline solution, randomized in blocks of four, were supplied by Astra Pharmaceuticals Pty Ltd. Each patient was allocated to one trial solution, identified only by a number, and a sealed copy of the treatment code was made available for emergency use if required. At the conclusion of the operative procedure, 20 mL of "trial solution" was injected into the pleural cavity through the pleural catheter.

Every 4 hours, regardless of degree of pain, patients were given further doses of trial solution through the

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pleural catheter. The solution was administered by the ward nursing staff with the patient supine and remaining so for 15 minutes after the injection. Drainage of the intercostal catheters was not altered at the time of injection; the suction was not disconnected, nor were the catheters clamped.

Supplementary doses of intramuscular papaveretum were given every 4 hours as deemed necessary by the nursing staff to maintain adequate pain relief. The number of doses and the total dose of narcotic were documented.

Assessment was performed 20 to 30 minutes after the intrapleural injections at 4, 24, 48, and 72 hours. Patients who had received intramuscular papaveretum less than 2 hours before assessment at 4 hours were excluded from that analysis. At all other assessment times, at least 3 hours had elapsed since the last dose of papaveretum. Patients were asked to assess their current resting pain level using a 10-cm linear analog scale [12] and part 2 of the McGill pain questionnaire [13]. Patients were assigned a rank pain score [3] by the medical officer:

1 = No pain
2 = Pain on deep breathing, coughing, or movement only
3 = Pain present: no narcotic required
4 = Pain present: narcotic required

Assessment of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate (PEFR) was performed by the physical therapist with the patient sitting. The FVC and FEV_1 were measured using a single Vitalograph bellows spirometer series R in the first 28 patients and a Vitalograph electronic-screen pneumotachograph spirometer (standard program issue 5) in the last 12 patients. The PEFR was measured using a Clement-Clarke miniwright peak flow minimeter. Assessment of pulse rate, blood pressure, respiratory rate, and somnolence was made by the medical officer. Somnolence was ranked on a five-point scale [14]:

1 = Oriented and initiates conversation
2 = Responds to all forms of stimulation and is well oriented, but feels sleepy and does not initiate conversation
3 = Responds to verbal commands and painful stimulation, but is disoriented and does not initiate conversation
4 = Responds to painful stimuli but not to verbal commands
5 = Unresponsive to verbal commands or painful stimuli

Removal of the pleural catheter was performed at the time of removal of the intercostal catheters or after 96 hours. Assessment was discontinued at the time of intercostal and pleural catheter removal or after 72 hours. At 6 to 12 weeks postoperatively, the patients were reassessed with respect to pulse rate, blood pressure, respiratory rate, FVC, FEV_1, and PEFR.

Table 1. Patient Characteristics[a]

Variable	Bupivacaine Group	Control Group
Sex (male : female)	15 : 5	18 : 2
Age (y)		
Mean	65.5	58.6
Range	41–76	21–73
Mean weight (kg)[b]	66.3	74.8
Diagnosis		
Non–small cell lung cancer	12 (60)	11 (55)
Mesothelioma	0	1 (5)
Benign pathology	5 (25)	7 (35)
Secondary malignancy	3 (15)	1 (5)
Operation performed[b]		
Single lobectomy	12 (60)	9 (45)
Two or more lobes resected	1 (5)	0
Wedge resection	6 (30)	4 (20)
Open biopsy	0	4 (20)
Pleurodesis ± pleurectomy	1 (5)	3 (15)

[a] Numbers in parentheses are percentages. [b] Significance: $p < 0.05$.

The data were analyzed by computer using a standard statistical package [15]. The χ^2 test was used to assess differences in contingency tables with the significance level set at 0.05. Differences between means were assessed from the relevant 95% confidence intervals (CI). Where patients were excluded from analysis, either because narcotics had been administered within the preceding 2 hours (4-hour assessment) or because the intercostal catheters had been removed, the total group size for analysis was taken as the remaining number of patients.

Results

There were 33 men and 7 women with a mean age of 62 years (range, 21 to 76 years). Table 1 lists the patient characteristics. Despite randomization, the bupivacaine group had a significantly lower mean weight than the control group. Significantly more patients in the bupivacaine group had a wedge or more of lung resected than in the control group.

At 4 hours postoperatively, 33 patients completed the linear analog scale; 29, the McGill questionnaire; and 36, respiratory function tests. Excluding those who had received papaveretum in the preceding 2 hours, results were available for 27 patients on the linear analog scale, for 24 on the McGill questionnaire, and for 30 on assessment of respiratory function.

One patient in the control group was still too drowsy to complete the McGill questionnaire at 24 hours, but all other patients completed the full assessment. Four patients had the intercostal and pleural catheters removed before the 48-hour assessment, and another 10 had the catheters removed before the 72-hour assessment.

Figure 1 shows the mean pain scores measured by the linear analog scale. The bupivacaine group had lower scores at all times, reaching significance at 4 hours, 24 hours, and 72 hours. The bupivacaine group also had significantly lower rank pain scores at 4 hours and 72 hours (Fig 2).

Two methods were used to calculate a pain score from the McGill questionnaire. The mean number of words chosen by the patient showed no significant differences between the two groups. However, the mean score of the words (ranked according to each word's position within its group) chosen by the experimental group was less than or equal to the control group at all times and significantly lower at 4 hours postoperatively (experimental group mean = 11.5, 95% CI = 4.8 to 18.2; control group mean = 20.5, 95% CI = 13.8 to 27.1).

There was no significant difference between the groups at any time in the absolute values of FVC, FEV_1, or PEFR or in the fall of these values from the preoperative levels. In the 31 patients whose respiratory function was assessed at 6 weeks postoperatively, all values remained significantly lower at that time compared with preoperative levels (Fig 3). These 6-week values were taken as the baseline, and all changes in breathing capacity were calculated from this level.

The bupivacaine group had a significantly smaller fall in FVC at 4 hours, 24 hours, and 48 hours (Fig 4). The bupivacaine group had a smaller fall in FEV_1 at all times (Fig 5), reaching significance at 4 hours and 48 hours. There was no significant difference in the fall in PEFR between the two groups at any time. There was no difference in the somnolence scores of the two groups at any time. Likewise, there was no difference in pulse rate, respiratory rate, or diastolic blood pressure. There was a significant difference in mean systolic blood pressure at 4 hours (bupivacaine group mean = 123 mm Hg, 95% CI = 114 to 132; control group mean = 139 mm Hg, 95% CI = 129 to 149).

The mean number of doses of papaveretum was the same for both groups. However, the mean total dose administered was significantly less in the bupivacaine group at 24 hours (bupivacaine group mean = 48.8 mg, 95% CI = 37.5 to 60.1; control group mean = 65.3 mg, 95% CI = 54.1 to 76.5 mg). This difference disappeared when the dose of papaveretum was calculated per kilogram of body weight.

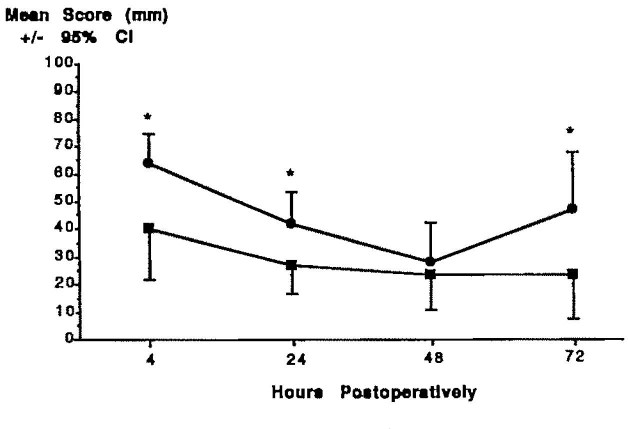

Fig 1. Linear analog pain scale scores. (CI = confidence intervals.)

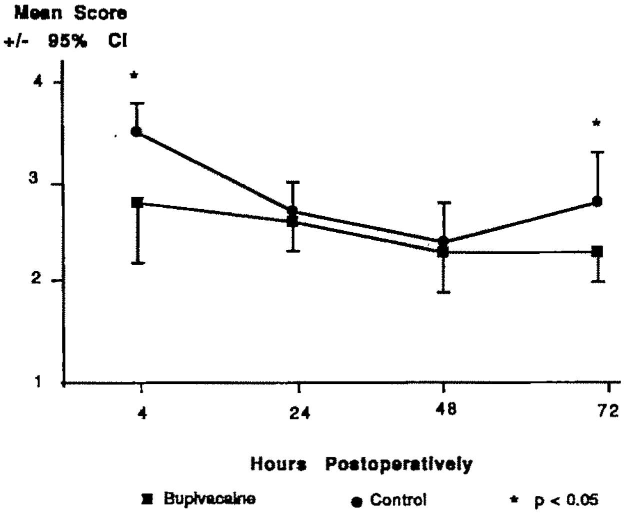

Fig 2. Rank pain scores. (CI = confidence intervals.)

In no patients did any complications develop that could be related to the pleural catheter or to the intrapleural administration of bupivacaine or saline solution. Specifically, there was no development of empyema, anaphylaxis, hypotension, or bradycardia. No patient had evidence of infection at the insertion site of the pleural catheter, and all catheters were removed without difficulty.

Comment

Thoracic and abdominal surgical procedures substantially decrease tidal volume, FVC, and FEV_1 during the early postoperative period [16–19]. This decrease can be minimized by reducing postoperative pain, thus improving the patient's ability to cough and clear secretions, maintain adequate ventilation, and cooperate with physical therapy. This in turn helps prevent atelectasis, collapse, and consolidation. Despite the development of other techniques, narcotics continue to be the mainstay of analgesia for patients after thoracotomy. It is, however, well recognized that the drugs cause major respiratory depression.

The use of intrapleural bupivacaine in this study was associated with lower pain scores at all times as assessed by linear analog scale and rank pain score. It appears that intrapleural bupivacaine, in the doses studied, is unable to give as complete an analgesic effect after thoracotomy as it can frequently provide after upper abdominal procedures [1, 3–6]. This probably results from the need to anesthetize higher intercostal nerves and from the more rapid removal of the local anesthetic from the pleural space through the intercostal catheters.

Several authors [20–24] have examined the long-term effects of thoracotomy and lung resection on respiratory function and have reported decreases in total lung capac-

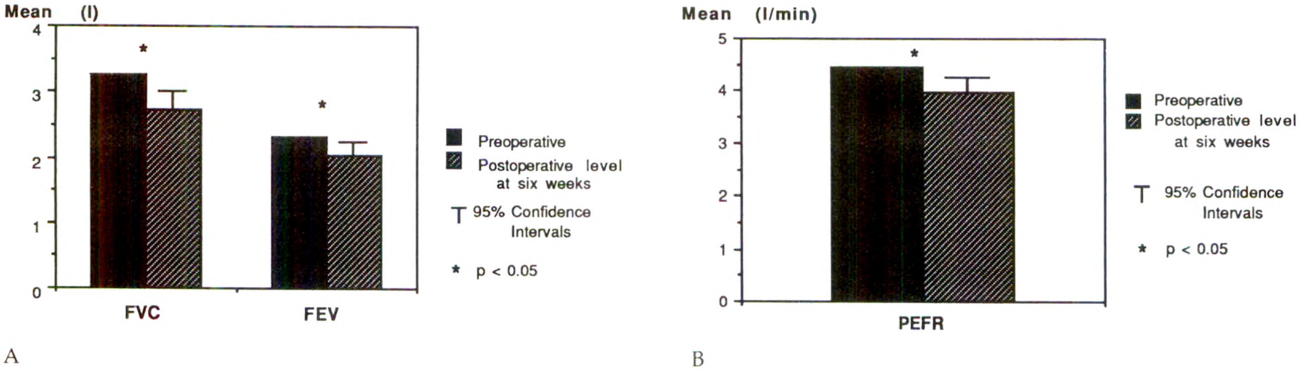

Fig 3. (A) Preoperative versus postoperative respiratory function at 6 weeks and (B) preoperative versus postoperative peak expiratory flow rate (PEFR) *at 6 weeks.* (FEV = *forced expiratory volume in 1 second;* FVC = *forced vital capacity.)*

ity and FVC related to the amount of lung tissue resected. Our results confirm a significant decrease in FVC, FEV_1, and PEFR that persists for at least 6 weeks after thoracic operations. As long-term postoperative lung function appears to be more accurately reflected by these readings than by preoperative readings, changes in FVC, FEV_1, and PEFR were calculated from the 6-week levels.

The total amount of papaveretum was lower in the bupivacaine group only for the first 24 hours postoperatively, and this difference disappeared when calculated on a weight basis. Before the commencement of this study, papaveretum was administered on a routine basis every 4 hours to all patients after thoracotomy. One possible explanation is that the nursing staff, unaware of which patients were receiving placebo and understanding the necessity for regular analgesia, continued to give intramuscular narcotics to all patients. This point could be clarified by a further study using patient-controlled analgesia with and without intrapleural bupivacaine.

An additional benefit of this technique is that patients receiving intrapleural bupivacaine can be managed safely in a thoracic or general surgical ward. The intrapleural bupivacaine can be administered by the ward nursing staff, thus obviating the need for admission to high-dependency or intensive care units.

Kambam and associates [11] recommended the use of bupivacaine with epinephrine, as lower plasma levels are obtained. Denson and co-workers [25], however, found no difference in the rate or extent of absorption of bupivacaine in monkeys given intrapleural bupivacaine with and without epinephrine. Although plasma levels were not measured, no patient in our study exhibited any symptoms or signs of toxicity using 0.25% bupivacaine without epinephrine.

Bruce and colleagues [5] tested the sensory level in 1 patient after thoracotomy who, after an intrapleural injection while sitting, experienced no pain relief and had a sensory block only from T-10 to T-12. After a later intrapleural injection while supine, he experienced complete pain relief with a correspondingly higher sensory level. Although a sitting position may be satisfactory for patients after an abdominal operation, to maximize analgesia at the level of a thoracotomy wound, the patient should be supine at the time of the injection and should remain so until the local anesthetic solution has had time to take effect.

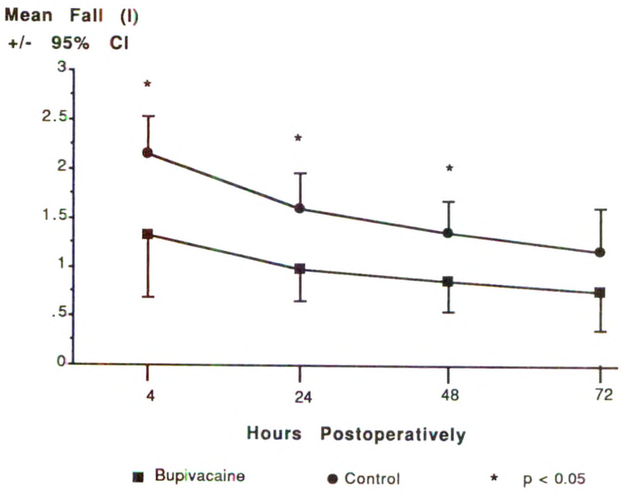

Fig 4. Fall in forced vital capacity from postoperative level at 6 weeks. (CI = *confidence intervals.)*

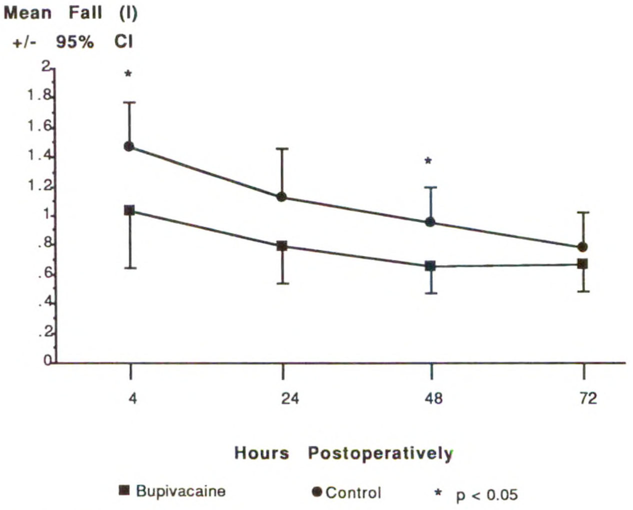

Fig 5. Fall in forced expiratory volume in 1 second from postoperative level at 6 weeks. (CI = *confidence intervals.)*

Symeng and co-workers [8], and Scheinin and associates [10] decided that clamping the intercostal catheters at the time of intrapleural injection was associated with an increased risk of developing atelectasis; therefore, they discontinued the suction only. Disconnecting the catheters carries the risk of prolonged periods without suction. Accordingly, in this study the intercostal catheters were not clamped, nor was suction discontinued. This reduced the potential risks to the patient but may have resulted in more rapid removal of the anesthetic solution from the pleural cavity. Rosenberg and colleagues [7] also left the intercostal catheters on suction and found no benefit using intrapleural anesthetic medication. However, no comment was made about the position of the patient at the time of injection. Symeng and associates [8], in a double-blind, controlled study of 15 patients, found significantly lower pain scores in the study group and commented that not clamping the chest tubes seemed to reduce the duration of action of the local anesthetic.

The results of our study support those of several authors [2, 8–11], who found analgesia was significantly improved after the intrapleural administration of bupivacaine in patients who had undergone a posterolateral thoracotomy. Intrapleural bupivacaine is a safe, easily administered form of analgesia that, when used in conjunction with intermittent doses of intramuscular narcotics, can provide better pain control with less respiratory depression than intermittent doses of narcotic analgesia alone.

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INVITED COMMENTARY

Control of postoperative pain has been a continuing concern of surgeons and anesthesiologists since the introduction of general anesthesia. In patients undergoing thoracic procedures, postoperative pain can result in significant loss of pulmonary function at a time when pulmonary reserve has been compromised by resection of functioning lung tissue. As we operate on a gradually aging population, the patients' pulmonary reserve is increasingly marginal or nonexistent. Although the effects of postoperative pain are temporary, the loss of pulmonary function during that time can result in serious complications or death. It has been estimated that thoracotomy alone without lung resection can temporarily reduce the maximum ventilatory volume by as much as 40%. The use of parenteral narcotics can control pain fairly well but is accompanied by respiratory depression and suppression of the cough reflex. Thus, there has been a continuing search for methods of pain relief that themselves do not contribute to depressed pulmonary function.

Mann and associates note that the forced vital capacity and 1 second forced expiratory volume were significantly lowered from preoperative values in all patients when measured 6 weeks postthoracotomy. However, in the early postoperative course both values were significantly better in the group treated with interpleural bupivacaine. Mann and associates do not comment on the relative incidences of postoperative pulmonary complications in the treatment and control groups. It is of interest that drainage through the intercostal catheters was not interrupted to permit the anesthetic agent to take effect. Nevertheless, the dosage given every 4 hours was effective.

In our hospital my colleagues and I have used a variety of techniques such as nerve blocks, freezing of the intercostal nerves at thoracotomy, and epidural catheters for prolonged use of low-dose opiates. Of these, the epidural administration of narcotics has been the most effective, but the technique carries all the risks of an indwelling epidural catheter. I think Mann and associates have described a very useful and effective alternative.

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Effects of Cardioplegic Solutions and Their Components on Human Saphenous Vein Contractility

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Cardioplegic solution administration into the vein graft is an established method to ensure cardioplegic distribution beyond coronary artery stenoses. The ultrastructural demonstration of severe endothelial damage after cardioplegic exposure suggests that intravenous cardioplegic administration can contribute to early and late graft thrombosis. The direct effect on human saphenous vein contractility of three cardioplegic solutions and their components was compared. A solution with 30 mmol/L K^+ and 82 mmol/L Na^+ produced intense venoconstriction. Lowering the potassium level to 10 mmol/L and increasing the sodium level to 92 mmol/L reduced its vasoconstricting action. A third solution with 16 mmol/L K^+, 16 mmol/L Mg^{2+}, and lidocaine caused venodilatation. Analysis of the single component effects showed that high potassium level, low sodium level, and the addition of lidocaine produced concentration-dependent vasoconstriction. High magnesium concentration resulted in vasodilatation. The present data suggest that cardioplegic solution composition may cause marked vasomotor effects on saphenous vein and thus influence its endothelial integrity. In the search for an "ideal solution" to the cardioplegic controversy, a venoconstrictor infusate should be avoided to improve patency rates of coronary artery bypass grafts.

(Ann Thorac Surg 1992;53:455–9)

Delivery of cardioplegic solution is heterogeneous in most clinical situations [1, 2], where coronary artery stenoses and myocardial hypertrophy cause coronary blood flow maldistribution. The principal limitation of the effectiveness of pharmacological cardioplegia is the ability to distribute and maintain the protective solution in all myocardial areas in amounts sufficient to exert its effects [3]. To circumvent this problem, cardioplegic solutions have been infused directly into saphenous veins after completion of the distal anastomosis.

Patency of aortocoronary saphenous vein grafts is influenced by native coronary anatomy, surgical techniques, and methods of harvesting and preparation of the vein graft for implantation. Venospasm resulting in intraluminal smooth muscle cell cytoplasmic protrusion causes endothelial damage and may predispose to short-term and long-term thrombosis of the implanted graft [4].

Cardioplegic solutions cause marked arterial endothelial damage [5, 6], and potassium has long been recognized as a vascular irritant [7]. Previous experiments from our laboratory showed that cardioplegic solution composition but not potassium concentration is responsible for coronary artery endothelial damage [8].

The present study was designed to examine if cardioplegic solutions and their components may produce saphenous vein vasoconstriction.

Material and Methods

A single segment of the human greater saphenous vein was removed for coronary artery bypass grafting. The terminal segment 2 to 3 cm in length before penetration of the fascia lata, which is less desirable for bypass purposes, was selected. Immediately after excision the tissue was placed into oxygenated Krebs solution and transported to the laboratory within 10 minutes. The vessels were cleaned of the adherent connective tissue and cut into spiral strips about 40 mm long and 2 to 3 mm wide.

The strips were superfused in a multiple tissue organ bath [9] at a rate of 2.5 mL/min with Krebs solution at 37°C, the composition of which was (in millimoles per liter): $NaHCO_3$, 25; NaCl, 118; KCl, 4.7; $CaCl_2 \cdot 2H_2O$, 2.5; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.17; and glucose, 5.6. The solution was gassed with 95% oxygen and 5% carbon dioxide. Changes in length were recorded with auxotonic transducers (ECTA, Milan, Italy) at a resting tension of 2 g after a 90- to 120-minute period of equilibration.

Responses were expressed as a percentage of the maximal response obtained with the bolus injection of a reference drug. Preliminary pilot experiments showed that 5 μg of 5-hydroxytryptamine caused near-maximal contraction, whereas 100 μg of nitroglycerin produced maximal relaxation of the human saphenous vein. Three

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Table 1. Composition of Cardioplegic Solutions[a]

Component	HKS	MKS	LKS
NaCl	82.5	110.0	92.5
KCl	30.0	16.0	10.0
$CaCl_2 \cdot 2H_2O$	1.0	1.2	1.0
$MgCl_2 \cdot 6H_2O$	. . .	16.0	. . .
$NaHCO_3$	26.8	10.0	26.8
Glucose	27.7	. . .	27.7
Mannitol	54.3	. . .	74.3
Lidocaine	. . .	0.05	. . .
gassed	95% O_2–5% CO_2	. . .	95% O_2–5% CO_2
pH at 37°C	7.4	7.6	7.4
Calculated osmolality[b]	363.6	323.6	363.6
Measured osmolality[b]	340	291	336

[a] Values are shown as millimoles per liter. [b] Shown as milliosmoles per kilogram of water.

HKS = high-potassium solution; LKS = low-potassium solution; MKS = magnesium and potassium solution.

different cardioplegic solutions were studied (Table 1). The University of Alabama Hospitals solution [10] was chosen as a prototype of the infusion solutions with high potassium concentration (30 mmol/L; HKS), because we use it clinically for the first cardioplegic injection. The St. Thomas' Hospital solution [11] was selected as an alternative solution containing magnesium in addition to a lower potassium concentration (MKS). We also tested a modified HKS. This solution has been formulated [12] to reduce coronary artery vasoconstriction [13] by lowering potassium content (LKS), and it is used in our department for subsequent cardioplegic administration. Institutional approval was obtained for the study protocol.

Because the three cardioplegic solutions varied in several ingredients, the effects of a single change in medium composition were studied by changing the superfusion from standard Krebs to a modified Krebs solution having a different content of a given constituent (sodium: 40, 60, 80, 100, and 120 mmol/L; potassium: 0, 5, 10, 20, and 30 mmol/L; magnesium: 2, 4, 8, and 16 mmol/L; bicarbonate: 0, 5, 10, 20, and 30 mmol/L; calcium: 0, 0.5, 1, 1.5, 2, and 2.5 mmol/L; or glucose: 0, 5, 10, 20, and 30 mmol/L) or with a new component added (mannitol: 20, 40, and 60 mmol/L; lidocaine: 0.01, 0.05, 0.2, 1, and 5 mmol/L).

The influence of hypothermia was studied by changing the temperature of the superfusing Krebs solution from 37° to 7°C; the actions of the cardioplegic solutions and their components were recorded under normothermic (37°C) as well as hypothermic (7°C) conditions.

Results are expressed as mean ± standard error. Each cardioplegic solution and its components were tested on 10 human saphenous vein rings obtained from at least 5 different patients. Statistical analysis was performed by analysis of variance for repeated measures. Multiple comparisons were made using the Scheffé *F* test. Only those differences with a probability of less than 0.05 were considered significant. The concentration-response relationship was examined by simple regression analysis. Regression curves were compared by analysis of covariance. Statistical analyses were performed on a Macintosh computer with the StatView II (Abacus Concepts, Berkeley, CA) program.

Results

After the superfusion had been started the tone of the saphenous veins decreased for 60 to 90 minutes before reaching a plateau. All experiments were performed in the 2 to 4 hours following the establishment of steady basal tone.

Superfusion with HKS (Fig 1) produced strong contraction of the saphenous veins, 83% ± 3.5% of the maximal contracting capacity (Fig 2). On the basis of the dose-response curve for potassium chloride, this effect was equivalent to that of KCl at 40 mmol/L. Superfusion with LKS evoked milder venoconstriction (see Fig 1), 19% ± 10.4% of maximum (see Fig 2), and equivalent to KCl at 13 mmol/L. On superfusion with MKS (see Fig 1) there was a fall in the basal tone to 35% ± 17.8% of the maximal relaxing capacity (see Fig 2). This response could be matched with magnesium chloride at 29.4 mmol/L.

The effects of vasoactive cardioplegic solution components are shown in Figures 3 through 6. A significant log dose-response regression was obtained for potassium, sodium, magnesium, and lidocaine. Venoconstriction was provoked in a concentration-dependent manner by an

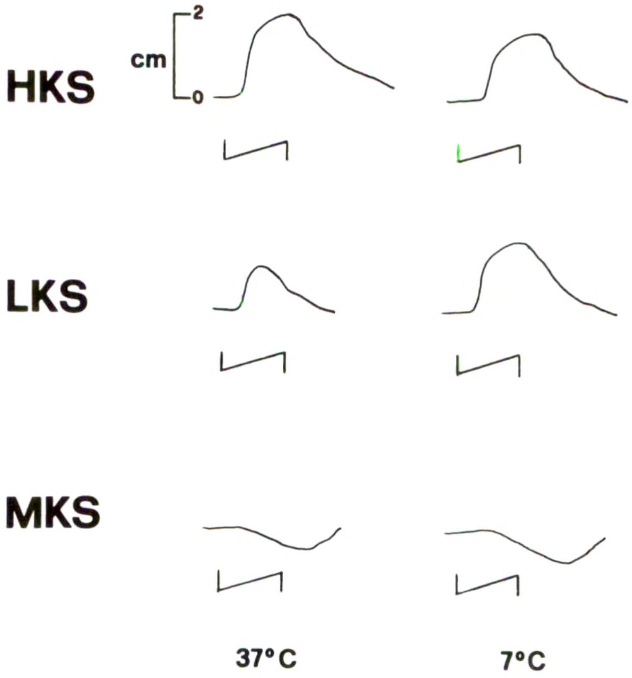

Fig 1. Human saphenous veins were superfused with three different cardioplegic solutions for 5 minutes (horizontal bars). *Cardioplegic solutions were tested under normothermic (37°C) and hypothermic (7°C) conditions.* Vertical bar *indicates actual auxotonic contraction or relaxation of the veins.* (HKS = *high-potassium solution;* LKS = *low-potassium solution;* MKS = *magnesium and potassium solution.)*

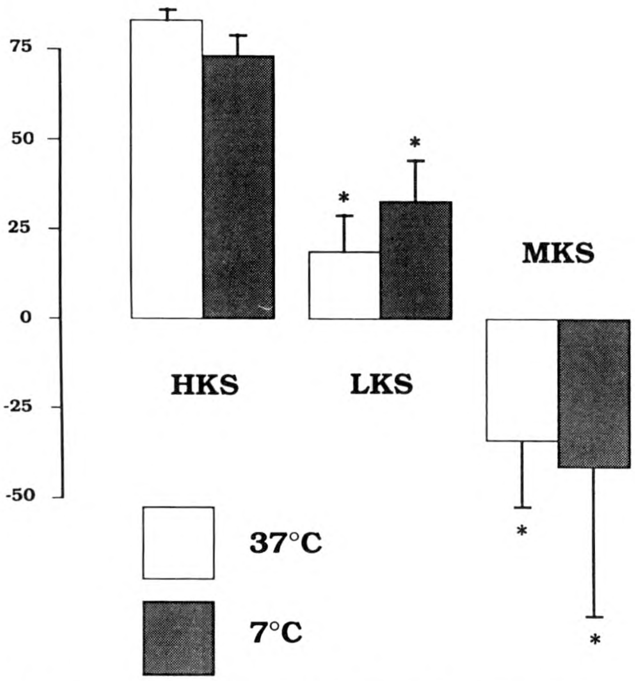

Fig 2. Effects of cardioplegic solutions on human saphenous veins with normothermic (37°C) and hypothermic (7°C) conditions. Contraction is expressed as a percentage of the maximal venoconstriction obtained with 5-hydroxytryptamine (vertical bar)*. Relaxation is expressed as a percentage of the maximal venodilatation produced by nitroglycerin.* Bars *indicate 1 standard error of the mean.* (HKS = *high-potassium solution;* LKS = *low-potassium solution;* MKS = *magnesium and potassium solution;* *p < *0.05 versus corresponding HKS group.)*

increase in potassium (y = 93.73logx − 75.81; $r = 0.84$; $F = 75$; $p < 0.0001$), by a decrease in sodium (y = −97.34logx + 203.86; $r = 0.90$; $F = 164.21$, $p < 0.0001$), or by the addition of lidocaine (y = 27.36logx + 70.44; $r = 0.55$; $F = 45.82$; $p < 0.0001$). High magnesium content produced vasodilatation (y = 16.44logx − 0.18; $r = 0.44$; $F = 7.27$; $p < 0.05$). Calcium, glucose, bicarbonate, and mannitol caused small and nonconsistent changes, which did not reach statistical significance.

Hypothermia (standard Krebs solution superfused at 7°C) produced a small dilating effect (5.8% ± 2.2%). This venodilating action of hypothermia did not uniformly influence the response to altered medium composition. Cooling the cardioplegic solution to 7°C reduced the contracting response to HKS by 11% and increased vasodilatation to MKS by 20%, whereas it enhanced the mild vasoconstrictor effect of LKS by 72%. Hypothermia significantly increased venoconstriction produced by potassium ($F_{\text{elevation}} = 4.82$; $p < 0.05$) (see Fig 3) and sodium ($F_{\text{elevation}} = 4.65$; $p < 0.05$) (see Fig 4). The vasodilating

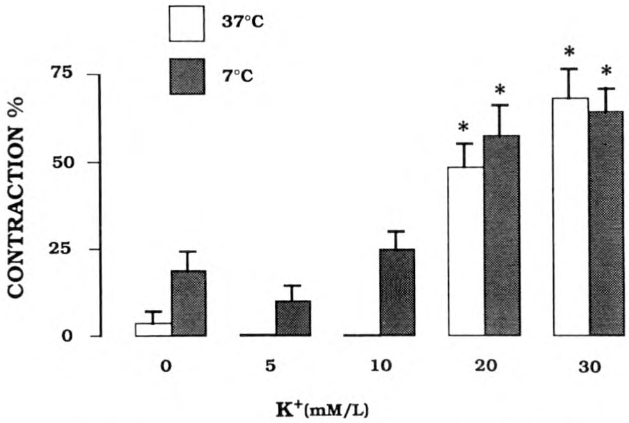

Fig 3. Effect of different potassium concentrations (modified Krebs solution containing 0, 5, 10, 20, and 30 mmol/L potassium chloride, K⁺*) on human saphenous veins at 37° and 7°C. Contraction is expressed as a percentage of the maximal response to 5-hydroxytryptamine.* Bars *indicate 1 standard error of the mean.(*p < 0.05 versus* K⁺ *at 0, 5, and 10 mmol/L at the corresponding temperature.)*

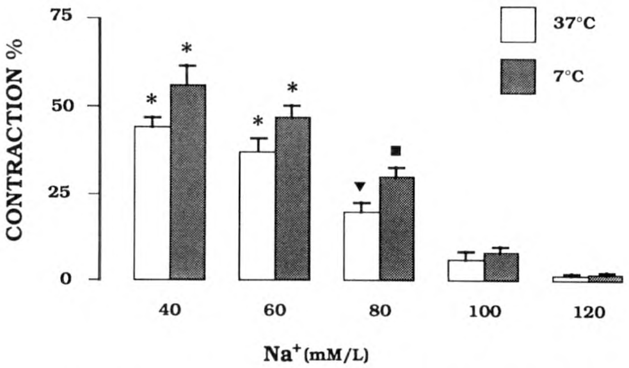

Fig 4. Effect of sodium concentration (modified Krebs solution containing 40, 60, 80, 100, and 120 mmol/L sodium chloride, Na⁺*) on human saphenous veins at 37° and 7°C. Contraction is expressed as a percentage of the maximal response produced by 5-hydroxytryptamine.* Bars *indicate 1 standard error of the mean. (*p < 0.05 versus* Na⁺ *at 80, 100, and 120 mmol/L at the corresponding temperature;* ▼p < *0.05 versus* Na⁺ *at 120 mmol/L at 37°C;* ■p < *0.05 versus* Na⁺ *at 100 and 120 mmol/L at 7°C.)*

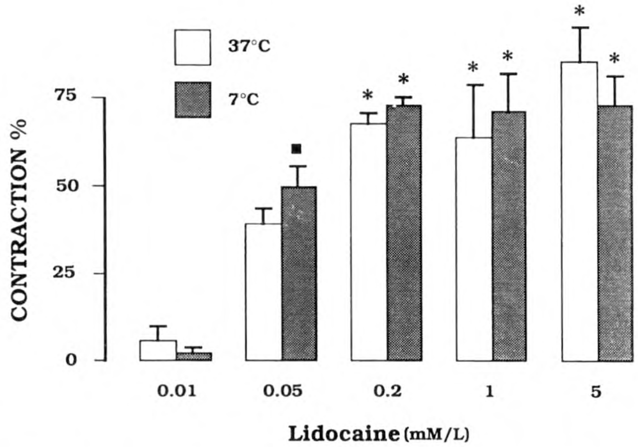

Fig 5. Effect of lidocaine (Krebs solution containing 0.01, 0.05, 0.2, 1, and 5 mmol/L lidocaine) superfused over human saphenous veins at 37° and 7°C. Contraction is expressed as a percentage of the maximal response to 5-hydroxytryptamine. Bars *indicate 1 standard error of the mean. (*p < 0.05 versus lidocaine at 0.01 mmol/L at the corresponding temperature;* ■p < *0.05 versus lidocaine at 0.2, 1, and 5 mmol/L at 7°C.)*

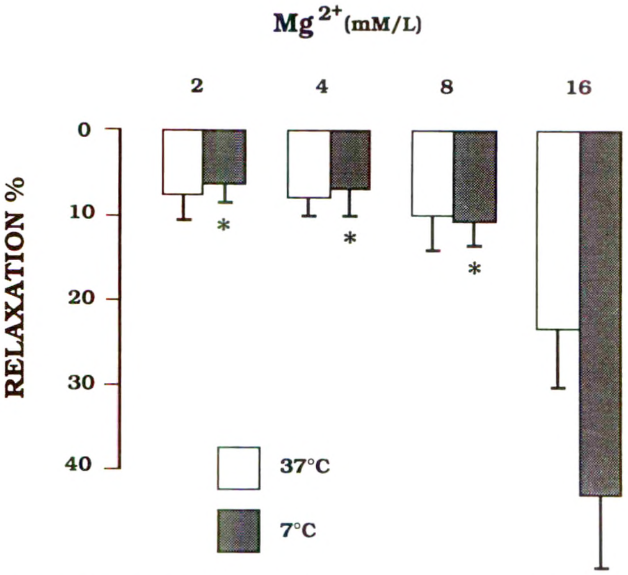

Fig 6. Effect of different concentrations of magnesium (modified Krebs solution containing 2, 4, 8, and 16 mmol/L magnesium chloride, Mg^{2+}*) on human saphenous veins at 37° and 7°C. Relaxation is expressed as a percentage of the maximal response to nitroglycerin.* Bars *indicate 1 standard error of the mean. (*p < 0.05 verus* Mg^{2+} *at 16 mmol/L at 7°C.)*

action of magnesium was increased by hypothermic conditions, especially at higher concentrations (F_{slope} = 4.41; $p < 0.05$) (see Fig 6).

Comment

The vein wall is extremely sensitive to dissection and manipulation and reacts to such stimuli with vigorous and prolonged contraction, which not only diminishes the luminal diameter but also results in protrusion of muscle cells into the lumen and into endothelial cells. Such cytoplasmatic extensions are particularly frequent in the immediate subendothelial area and cause elevation, separation, or desquamation of the endothelial cell monolayer [4]. Veins stored in blood alone demonstrate the greatest vessel wall contraction and endothelial cell loss. Pretreatment with the vasodilator papaverine greatly reduces vein graft endothelial cell loss due to contraction [14].

Severe endothelial damage with consequent platelet deposition and thrombus formation is the main cause of aortocoronary vein grafts occlusion within the first month [15]. Despite endothelial regeneration, the initial endothelial damage at operation initiates a chronic platelet–vessel wall interaction, which promotes smooth muscle cell and connective tissue proliferation, eventually leading to late graft stenosis and occlusion [15]. Therefore, the preservation of the structural integrity of the vein endothelium appears to be critical for graft patency.

Vasomotor effects of cardioplegic solutions have been described in bovine conductive coronary arteries [13], and vasoconstricting solutions should be avoided to favor more effective myocardial protection [2].

The present data show that alterations of ionic and pharmacological environment caused by cardioplegic infusion are responsible for critical changes in saphenous vein tone. The administration of a high potassium solution (HKS) causes strong venoconstriction corresponding to 83% of the maximal contracting capacity. This effect may compromise homogeneous cardioplegic delivery and cause damage of the vein wall. A solution with different composition (MKS) has a dilating action on saphenous veins. Formulation is therefore critical for the vasomotor effect on the vein grafts. These solutions differ in several ingredients, and their vasoactivity is the result of the interaction of many factors. The vasoconstricting effect of HKS may be attributed to its high potassium and low sodium concentration. In fact, lowering potassium and increasing sodium concentration (LKS) significantly reduces the constrictive effect on saphenous veins and is responsible for coronary artery vasodilatation [16]. Among the various components, at the concentration used in cardioplegia, high potassium levels, low sodium levels, and lidocaine produced venoconstriction, whereas magnesium evoked venodilatation. However, it cannot be excluded that other ingredients with no direct vasoactivity might influence the final effect of cardioplegic solutions on saphenous veins.

Local anesthetic agents may confer additional protection during intraoperative cardioplegia [17]. In our experiments, lidocaine demonstrated a powerful vasoconstrictor effect on human saphenous veins, which is not evident on coronary arteries [18]. Therefore, it should not be added to a cardioplegic solution, especially if this is administered directly into the graft.

Hypothermia reduced the coronary artery constricting effect of some cardioplegic solutions and components [2, 13], whereas it increased saphenous vein constriction induced by certain cardioplegic infusates. The increased contractility of venous smooth muscle observed during hypothermic conditions is similar to the positive myocardial inotropic effect of hypothermia [19] and may be accounted for by an increased availability of intracellular calcium [20]. On this basis, cooling the solution does not counteract the venoconstrictor effect, and a vasodilating agent should be used.

The different reactivity between bovine coronary arteries and human saphenous veins might be attributed to species differences, but human conductive coronary arteries obtained from transplant recipient hearts reacted to cardioplegic solutions similarly to the corresponding bovine vessels (Chiavarelli M, unpublished results). The pattern of human saphenous vein contractile activity does not completely fit the known scheme of vascular smooth muscle reactivity to a change of ionic or pharmacological environment. Therefore, each cardioplegic solution component has to be tested on saphenous veins when an intravenous administration is considered.

Myocardial protection beyond coronary artery obstructions may be improved by performing the proximal anastomosis first and then administering another dose of cardioplegia after each distal anastomosis [3]. However, the usefulness of such a procedure seems to be limited by a venoconstrictor cardioplegic solution, because flow through the graft will be reduced. Conversely, a venodilating solution should be considered advantageous, because it might favor a more uniform cardioplegic distribution.

Direct infusion into the saphenous vein after completion of the distal anastomosis may obviate this problem, but strong constriction of the vein wall has a potentially harmful effect, especially if the cardioplegic solution produces direct anatomic [21] or functional [22–24] damage of the endothelium.

Retrograde cardioplegia results in myocardial cooling distal to coronary obstructions and preserves myocardial function in all areas [25]. Coronary sinus cardioplegia prevents the potentially harmful effect of infusing solutions into the vein graft. However, the effect of cardioplegic solutions and their components on cardiac veins should be tested. Intraoperative cardiac protection should take into consideration preservation of integrity of the saphenous veins, because they become an integral part of the conductive coronary vascular bed.

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Palliative Intubation for Dysphagia in Patients With Carcinoma of the Esophagus

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One hundred seven consecutive patients seen over a 6-year period with dysphagia secondary to advanced primary carcinoma of the esophagus underwent intubation. One hundred five patients underwent pulsion intubation. In 2 patients pulsion intubation was not possible, and laparotomy and traction intubation was performed. For the intubated group there were 65 men and 40 women (ratio, 1.6:1), with a mean age of 71.3 ± 10.5 years (range, 36 to 92 years). Of the 105 patients who had pulsion intubation, a perforation developed in 11 (10.5%), which was responsible for the death of 4 patients (3.8%). A further 3 patients died of malignant cachexia, which resulted in an overall mortality of 6.7%. Late complications included tube displacement (4 patients; 3.8%) and tube obstruction (32 patients; 30.5%). Tube obstruction was due to advancement of malignant disease in 26 patients (81.2%) and food bolus impaction in the remaining 6 patients (18.8%). Pulsion intubation for advanced carcinoma of the esophagus can be performed with a low morbidity and early mortality. However, there is a substantial long-term morbidity of tube obstruction in almost a third of survivors.

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Despite advances in therapy, the 5-year survival rates for carcinoma of the esophagus remain low. This is in part due to the late disease presentation, which makes surgical resection inappropriate. Many lesions of the lower esophagus and cardia are unsuitable for curative resection at presentation and need some form of palliative procedure to relieve obstruction [1]. Surgical bypass in such patients has lost favor because of the unacceptable high morbidity and mortality [2]. Palliative dilation with or without radiotherapy has been abandoned because malignant strictures were found to recur within a mean period of 2 weeks [3]. More recently other modalities such as neodymium:yttrium-aluminum garnet laser therapy [4–6], thermocoagulation, and endoesophageal irradiation [7, 8] have become available but are still undergoing assessment. The mainstay of palliation for malignant dysphagia remains esophageal intubation. Nevertheless, the problem still remains in identifying a method for esophageal intubation that minimizes the risk to the patient but can successfully relieve dysphagic symptoms. Reports have described the use of both pulsion and traction methods but have indicated a higher associated mortality and morbidity with the latter technique. The preferred method now is an endoscopic pulsion technique, which has been described using a flexible introducer [9], a flexible esophagoscope with introducer [10], or a rigid esophagoscope [11]. We employ a technique of pulsion intubation using a rigid esophagoscope, which we have recently described [12]. All intubations now done in our unit are performed under general anesthesia using an endoscopic technique with an Atkinson tube. We describe our experience in a group of 107 consecutive patients all with primary malignancies of the esophagus.

Patients and Methods

Between January 1984 and December 1990, 105 patients underwent palliative pulsion intubation of the esophagus for the relief of dysphagia. In 2 further patients it was not possible to intubate the esophagus by the pulsion technique. In these 2 patients the esophagus was successfully intubated from below by traction through a gastrotomy. For the intubated group there were 65 men and 40 women (ratio, 1.6:1), with a mean age of 71.3 ± 10.5 years (range, 36 to 92 years). Only patients with primary esophageal malignancies were included in this study. In the 107 patients, 52 had adenocarcinomas and 55 had squamous cell carcinomas. In 11 patients the carcinoma was in the upper third of the esophagus, in 53 patients it was in the middle third, and in 43 patients it was in the lower third of the esophagus. The indication for palliative intubation was advanced esophageal disease on preoperative staging in 73 patients, T4 or M1 disease after laparotomy in 20, recurrence after radiotherapy in 10, and recurrence after esophagectomy in 4. Sixty-four patients (59.8%) had intubation after clinical examination, ultrasound, and computed tomographic scanning had demonstrated advanced disease that was unsuitable for curative resection.

All patients underwent pulsion intubation under general anesthesia, using a modified rigid esophagoscope as previously described [12], unless they had severe cervical osteoarthritic disease. In these patients, when the neck could not be safely manipulated, a technique similar to that described by Boyce [10] was employed. All patients

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received a lateral neck and chest roentgenogram in the first 24 hours after intubation to screen for perforation of the esophagus.

Results

Of the 107 patients, intubation was undertaken in 105 patients (98.1%) by the two pulsion techniques. In 2 patients (1.9%), intubation was finally achieved by laparotomy, gastrotomy, and traction of the intubating tube from below. Both patients were discharged from the hospital with a mean hospital stay of 6.5 ± 0.7 days, without complications.

Early Complications for Pulsion-Intubated Patients

Of the 105 patients who had pulsion intubation, 3 patients (2.9%) needed to be returned to the operating theater within 24 hours because the tube needed repositioning. In 2 of these patients this was due to a high tube that could not be tolerated by the patient. In the third patient, proximal displacement of the tube had occurred. In a further 11 patients (10.5%) perforation occurred during insertion. This was managed conservatively in all cases by intravenous antibiotics, parenteral fluid and electrolytes, and insertion of an intercostal drain if a fluid collection was present on a chest roentgenogram. Perforation was responsible for the death of 4 patients (3.8%). The remaining 7 patients recovered to be discharged home. In a further 3 patients, death occurred as a result of malignant cachexia, which resulted in an overall mortality of 7 patients for the pulsion-intubated group (6.7%).

Postoperatively the patients were allowed a soft food diet. We have previously found that a liquid diet is both unnecessary and unpalatable in a group of patients who are already anorexic.

The mean hospital stay was 4.8 ± 2.1 days for patients who received pulsion intubation.

Late Complications

In 36 patients (34.2%), Atkinson tube-related complications were identified. These occurred between 2 weeks and 7 months after discharge.

TUBE DISPLACEMENT. In 4 patients distal tube displacement occurred. In 2 of these patients the Atkinson tube was unrecoverable. In 1 patient it was found lying in the stomach, and in the second patient it had migrated to the large bowel without complications (Fig. 1). In both patients new Atkinson tubes were inserted by the pulsion method. In a further 2 patients the Atkinson tube was successfully repositioned without complications.

TUBE OBSTRUCTION. In 32 of 105 patients (30.5%), tube obstruction was a problem and presented itself as dysphagia or aspiration. In 26 patients (24.8%), this was due to advancement of the esophageal carcinoma causing obstruction of the lumen of the intubating tube. The management of these patients is outlined in Figure 2. In 16 of these patients it was replaced with a second Atkinson tube, and in 3 patients another type of tube was employed, whereas 7 patients were referred for radiotherapy. In 10 of 26 patients with tumor obstruction, repositioning was sufficient to relieve the esophageal obstruction.

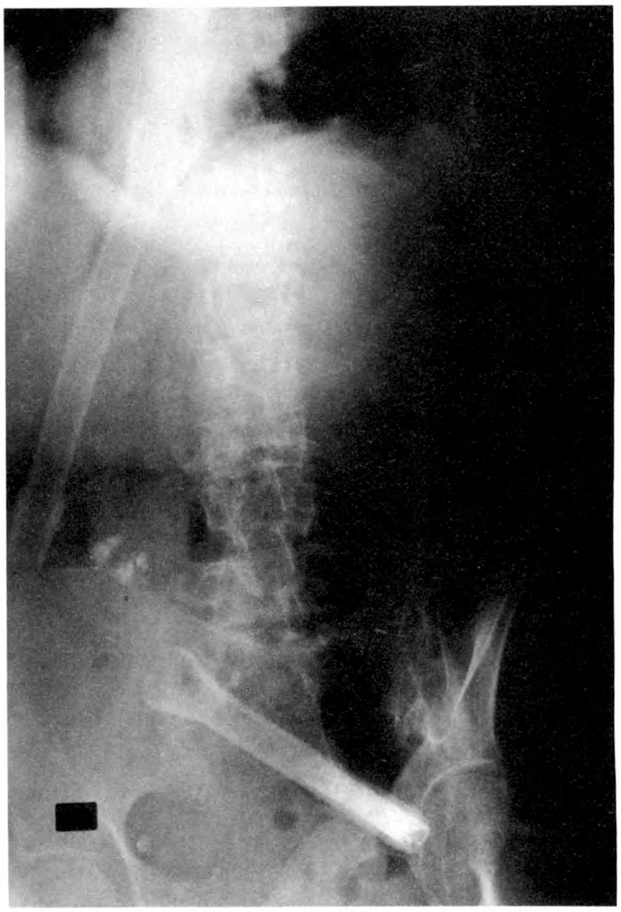

Fig 1. Plain abdominal radiograph showing a distally displaced Atkinson tube lying in the large bowel, with a Celestin tube lying in the correct position across the obstructing tumor in the esophagus.

Six patients with dysphagia were found to have tube obstruction secondary to food bolus impaction. In 2 patients the tube was repositioned because tumor could be seen, which could have caused obstruction at a later date.

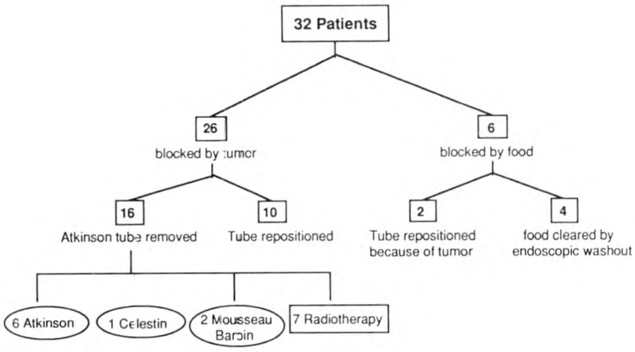

Fig 2. The management of tube obstruction.

In the remaining 4 patients endoscopic washout and suction of food debris was sufficient to relieve dysphagia.

Survival

Of the 96 patients who were discharged from the hospital having undergone pulsion intubation, 77 patients (80.2%) were followed up. The mean survival was 5.1 ± 4.7 months (range, 15 days to 22 months).

Comment

In patients who have incurable carcinoma of the esophagus, the minimal procedure that achieves relief of distressing dysphagia is the goal. The technique of peroral pulsion intubation has gradually gained favor over laparotomy and traction intubation with its associated high mortality. There have been many recent modifications of the intubating technique, and previous studies have examined a heterogenous group of patients with both primary and secondary tumors of the esophagus. We have endeavored to establish the risks of pulsion intubation of the esophagus for patients with primary esophageal malignancies.

The most severe complication remains perforation of the esophagus. The rate of perforation for our series was 10.5%, which compares favorably with that previously reported of 8% to 12.5% [13, 14]. Perforation was responsible for the death of 4 patients, whereas the remaining 7 patients survived to be discharged. The procedural mortality has been reported between 2% and 16% [13–16], which reflects not only differences in intubation techniques but also patient groups. In our series the procedure-related mortality was 6.7%, which is higher than the 5% reported by Den Hartog Jager and associates [13]. However, in their series of 200 patients, only 77 patients had primary carcinoma of the esophagus, whereas 25 had bronchogenic carcinomas and 98 had gastric cancers, which makes direct comparison with our patients unreliable.

It is notable that in only 1 patient was proximal migration of the Atkinson tube a complication. This can be largely attributed to its design with a shouldered distal end. Nevertheless, distal migration occurred in 4 patients, and in 2 of these patients the tube was not recovered. Techniques have been described [13, 17] for the removal of the Celestin tube from the stomach and esophagus, because of the reported risks of tube fragmentation and subsequent small bowel obstruction and jejunal perforation [18, 19]. However, no such problems have been reported for the Atkinson tube, which is made of nondegradable silicone rubber, unlike tubes of the Celestin design, which are made of latex rubber. In the presented series, we encountered no gastrointestinal complications in 2 patients with nonrecoverable Atkinson tubes.

Other complications such as hemorrhage were not encountered in our patients and have only rarely been reported in previous studies [20, 21]. Acid reflux similarly was not a major problem in our patients, which has been borne out in other series [14, 22], but it may cause stricture formation above the intubating tube and require dilation [22] together with medical therapy to neutralize or diminish gastric acid production.

In terms of symptom relief, the majority of our patients had almost complete relief of their dysphagia. Dysphagia, as it is a subjective measure, is difficult to quantify, although Atkinson and Ferguson [9] have suggested a scoring system from 0 to 4. Intubation undoubtedly causes some degree of discomfort to the patient, but all our patients were able to be discharged on a near-normal diet. We have found a liquid diet both unpalatable and unnecessary. Only 6 patients (5.7%) were found to subsequently have development of food obstruction of their tubes, whereas in the remainder, advancement of their cancer was the underlying cause. Laser therapy with the neodymium:yttrium-aluminum garnet laser is currently undergoing assessment as an alternative or adjunct therapy to intubation. Apart from requiring both expertise and resources, it has the disadvantages that submucosal lesions and compression from extrinsic masses are unsuitable for treatment. Initial results from laser therapy were reportedly good, with up to one third of patients having complete relief of dysphagia and returning to a normal diet. Although there was no significant difference in the survival between laser and tube patients, 64% of patients treated by laser needed further treatment after initially good results. In two thirds of these patients, further laser therapy was possible, but in the remaining one third, obstruction was caused by fibrous stricturing or extrinsic compression, which necessitated the insertion of a prosthetic tube [23]. However, laser therapy may be used as an adjunct to prosthetic tube insertion. In 26 patients in our series, tube obstruction resulted from tumor growth, which was managed by either repositioning or removal followed by replacement or radiotherapy. In these patients it may be appropriate to leave the tube in situ and destroy the obstructing tumor with laser therapy [22].

In conclusion, we found that intubation of 105 patients using a pulsion technique was associated with a low mortality and early morbidity, but a substantial long-term morbidity of tube obstruction. The intubating tube provided good relief of dysphagia, with all patients discharged returning to a near-normal diet. It is a technique that, although simple in design, requires experience in endoscopy and dilation, and should therefore be performed by appropriately skilled individuals if potentially fatal complications are to be avoided.

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Adverse Effect of Prearrest Hypothermia in Immature Hearts: Rate Versus Duration of Cooling

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It has been suggested that rapid cooling before the induction of arrest may be harmful to the newborn myocardium. The objective of this study was twofold: (1) to evaluate whether prearrest rapid cooling is indeed detrimental to myocardial recovery and (2) if so, to evaluate whether the adverse effect of prearrest hypothermia is dependent on the rate of cooling or the total duration of cold perfusion. After an initial stabilization period isolated Langendorff hearts (n = 5 per group) from neonatal piglets (5 to 7 days old) were randomized to four groups: group 1, 5 minutes of rapid cooling to 15°C; group 2, 20 minutes of slow cooling to 15°C; group 3 and group 4, rapid and slow cooling, respectively, with the addition of St. Thomas cardioplegic solution. All groups were then subjected to 2 hours of ischemia at 15°C followed by 30 minutes of reperfusion at 38.5°C. Postischemic recovery of left ventricular developed pressure was significantly greater in group 1 versus group 2 (80% ± 3% versus 61% ± 2%; $p < 0.05$) and in the presence of cardioplegia, group 3 versus group 4 (72% ± 3% versus 57% ± 3%; $p < 0.05$). The increase in left ventricular end-diastolic pressure was significantly less in group 1 versus group 2 (8% ± 5% versus 33% ± 7%; $p < 0.01$). Myocardial adenosine triphosphate content recovery correlated with ventricular recovery. To evaluate the second objective, hearts were divided into three groups: group 1, rapid cooling (5 minutes); group 2, rapid cooling (5 minutes) + cold perfusion (15 minutes) at 15°C; and group 3, slow cooling (20 minutes). Postischemic recovery of left ventricular developed pressure was significantly greater in group 1 versus groups 2 or 3 (80% ± 3% versus 64% ± 5% or 61% ± 2%, respectively; $p < 0.05$). Rise in left ventricular end-diastolic pressure was significantly less in group 1 (8% ± 5%) versus group 2 (43% ± 14%) or group 3 (33% ± 7%) ($p < 0.05$). Creatine phosphate levels correlated directly with greater recovery of ventricular function in group 1. The results demonstrate that (1) rapid cooling is not detrimental and in fact offers better protection than slow cooling, (2) the detrimental effect of cooling appears to be related to the duration and not the rate of cooling, and (3) cardioplegia does not provide any additional protection. Therefore, prolonged prearrest hypothermic perfusion is detrimental to the newborn heart and should be avoided.

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Myocardial hypothermia reduces the severity of ischemic damage, and it has become of critical importance in protecting the ischemic myocardium during cardiac operations [1–3]. Repair of congenital lesions in early life often requires a period of deep hypothermic circulatory arrest. The latter involves a period of cold systemic perfusion on cardiopulmonary bypass before circulatory arrest is established.

The basis for this study arose from clinical observations [4, 5] that noted that rapid cooling of the newborn myocardium appeared to induce contracture either resulting in injury itself or adversely influencing the subsequent period of circulatory arrest. The objective of the present study was twofold: (1) to experimentally evaluate whether rapid cooling before the induction of arrest is indeed detrimental to myocardial recovery and (2) if so, to evaluate whether the adverse effect of prearrest hypothermia is dependent on the rate or duration of cold perfusion. The effect of single-dose cardioplegia on myocardial protection of the newborn heart was also assessed. Considerable controversy surrounds the ability of cardioplegic solutions to protect the immature myocardium, and it has been suggested that hypothermia alone may provide adequate protection during cardiac arrest [6–9].

Material and Methods

Preparation

Hearts were obtained from neonatal piglets (age, 5 to 7 days). All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

The animals were premedicated with intramuscular ketamine (30 mg/kg), xylazine (5 mg/kg), and atropine (0.2 mg/kg). After intravenous administration of sodium

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Table 1. Composition of the Coronary Perfusates[a]

Constituent	Krebs-Henseleit Bicarbonate Buffer	St. Thomas' Hospital Cardioplegic Solution No. 2
NaCl	118.5	110.0
$NaHCO_3$	25.0	10.0
KCl	4.8	16.0
KH_2PO_4	1.2	. . .
$MgSO_4 \cdot 7H_2O$	1.2	. . .
$MgCl_2 \cdot 6H_2O$	. . .	16.0
$CaCl_2 \cdot 2H_2O$	2.4	1.2
pH	7.4	7.8

[a] All values except pH are in millimoles.

pentobarbital (20 mg/kg) and heparin (500 U/kg), a median sternotomy was performed and hearts were rapidly excised and placed in an ice-cold perfusion medium. Hearts were then connected to the aortic cannula of a Langendorff perfusion apparatus.

Perfusion Media

The standard perfusion medium used was Krebs-Henseleit bicarbonate buffer maintained at 38.5°C and a hydrostatic pressure of 80 cm H_2O. The perfusate was bubbled with a mixture of 95% oxygen and 5% carbon dioxide at a pH between 7.40 and 7.44. The cardioplegic solution used was St. Thomas' Hospital No. 2. Compositions of the individual perfusates are shown in Table 1.

Left Ventricular Pressure Measurements

Isovolumetric pressures were measured with a fluid-filled balloon inserted into the left ventricular cavity through the atrium. The balloon was then connected by a fluid-filled polyethylene catheter to a pressure transducer, and pressures were transcribed on a Grass polygraph chart recorder. The volume of the balloon was adjusted to give an end-diastolic pressure (LVEDP) of 12 to 15 mm Hg. Continuous recordings were made of heart rate, LVEDP, and left ventricular developed pressure (LVDP). A differentiator provided recordings of the first derivative of developed pressure (dP/dt).

Biochemical Determination

Full-thickness biopsy specimens were obtained from the right and left ventricular free wall and immediately frozen in liquid nitrogen. The samples were then stored at −80°C until assays for adenosine triphosphate (ATP) and creatine phosphate (CP) were performed by the method of Biochemical Research Assays Limited, York University, Toronto [10].

Perfusion Protocol

COMPARISON OF DIFFERENT RATES OF COOLING. The following experiments were performed to evaluate whether rapid cooling before the induction of arrest is indeed detrimental to the newborn heart and impairs recovery (Fig 1). Immediately after aortic cannulation, the piglet heart was perfused in a Langendorff perfusion model at 38.5°C for a 30-minute stabilization period. During this steady-state period, control values for left ventricular pressure measurements were taken. Hearts were then randomly assigned to four groups (n = 5 per group): group 1 hearts were rapidly cooled over 5 minutes to 15°C. In the rapid cooling groups, hearts were cooled to 20°C in 3.0 ± 0.2 minutes and to 15°C in the remaining 2 ± 0.3 minutes. Group 2 hearts were slowly cooled over 20 minutes to 15°C. Slow cooling of hearts consisted of cooling to 20°C in 15.0 ± 0.3 minutes and to 15°C in the remaining 5.0 ± 0.3 minutes. Group 3 hearts were rapidly cooled as in group 1 except for the addition of a single dose of St. Thomas cardioplegic solution immediately after the cooling period. The solution was administered for 2 minutes at a perfusion pressure of 80 cm H_2O. Group 4 hearts were slowly cooled as in group 2 except for the addition of a single dose of St. Thomas solution as above. All hearts were then subjected to hypothermic (15°C) global ischemia for 120 minutes. During ischemia, myocardial temperature was continuously measured with an intramyocardial temperature probe and maintained at 15°C. After the ischemic phase, all hearts of every group were reperfused for 30 minutes at 38.5°C. Hemodynamic pressure measurements were taken at the end of reperfusion to assess the extent of recovery. The protocol used for this experiment was then repeated to allow for serial left ventricular free wall biopsy specimens to be taken at control, end of cooling (prearrest), end of ischemia, and at the end of reperfusion periods. All samples were then immediately frozen at −80°C for ATP and CP assays.

RATE VERSUS DURATION OF COOLING. The following experiments were performed to evaluate whether the adverse effects of prearrest hypothermia are dependent on the rate

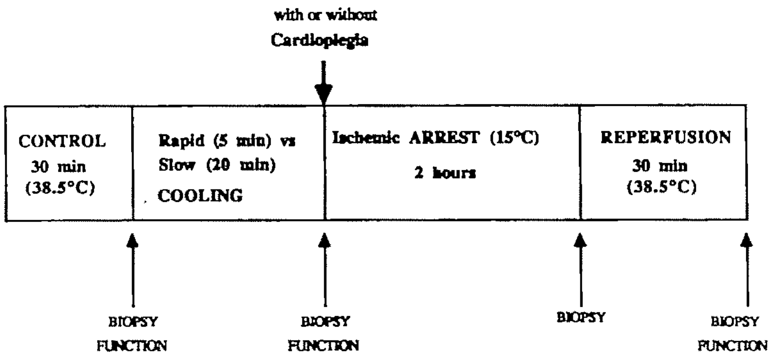

Fig 1. Experimental protocol (n = 5 per group) for comparison of different rates of cooling.

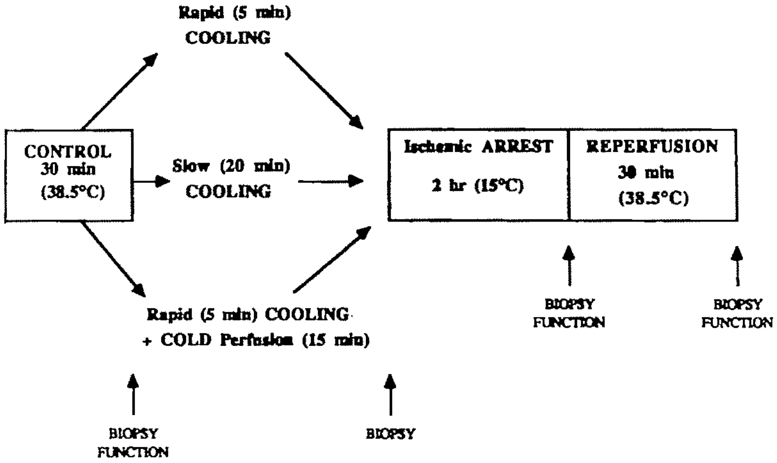

Fig 2. Experimental protocol (n = 5 per group) for rate versus duration of cooling.

or duration of cooling (Fig 2). Hearts were divided into three groups. All hearts were subjected to an initial stabilization period of 30 minutes of perfusion at 38.5°C. After this, group 1 hearts were rapidly cooled over 5 minutes to 15°C. In group 2, hearts were rapidly cooled as in group 1 with the addition of 15 minutes of cold perfusion at 15°C. Group 3 hearts were slowly cooled over 20 minutes to 15°C. All hearts were then subjected to 120 minutes of hypothermic global ischemia at 15°C, after which hearts were reperfused for 30 minutes at 38.5°C.

Hemodynamic measurements were continuously recorded throughout the experiment. Right ventricular biopsy specimens for measurement of CP content were also taken at different periods of the perfusion sequence: control, end of cooling (prearrest), end of ischemia, and end of reperfusion.

Expression of Results

Recovery of ventricular pressure indices were expressed as a percentage of preischemic control values. Levels of ATP and CP were expressed as micrograms per gram of dry weight of myocardial tissue.

Statistical Analysis

Data are reported as mean ± standard error of mean. Comparisons for any index between groups were performed using a Student's unpaired t test. Analysis of variance was used for multiple comparisons within groups. A probability of less than 5% ($p < 0.05$) that a difference between groups occurred by chance was accepted as being statistically significant.

Results

Different Rates of Cooling

VENTRICULAR FUNCTION. The data on the recovery of ventricular function after ischemia in the four study groups are presented in Table 2. The hemodynamic stability of the model was assessed by perfusing hearts for 180 minutes with Krebs buffer at 38.5°C. No statistically significant changes in baseline measurements occurred until after 150 minutes. In these studies, hearts were perfused for a maximum of 90 minutes (control, cooling, and reperfusion), well within the stability limits of the preparation.

Postischemic recovery of LVDP (Fig 3) was significantly greater with rapid cooling in group 1, as compared with slow cooling in group 2 (80% ± 3% versus 61% ± 2%; $p < 0.001$). This difference was maintained with the addition of cardioplegia; the recovery of LVDP was 72% ± 3% in group 3 versus 57% ± 3% in group 4 ($p < 0.01$). The results for +dP/dt and −dP/dt revealed that in both instances there was greater recovery with rapid cooling both in the absence and presence of cardioplegia. Thus, after 2 hours of ischemia, +dP/dt recovered to 77% ± 5% in group 1 versus 61% ± 4% in group 2 ($p < 0.01$) and 71% ± 5% in group 3 versus 57% ± 4% in group 4 (not

Table 2. Comparison Between Rapid and Slow Cooling With or Without Cardioplegia[a]

Group	Heart Rate	LVDP	LVEDP	+dP/dt	−dP/dt
1. Rapid cooling	83 ± 4	80 ± 3[b]	8 ± 5[b]	77 ± 5[b]	84 ± 4[b]
2. Slow cooling	94 ± 3	61 ± 2	33 ± 7	61 ± 4	63 ± 2
3. Rapid + CPG	90 ± 4	72 ± 3[c]	36 ± 12	71 ± 5[c]	74 ± 4
4. Slow + CPG	88 ± 6	57 ± 3	33 ± 18	57 ± 4	62 ± 3

[a] All data expressed as percent mean ± standard error of the mean. [b] $p < 0.05$ versus slow cooling group (group 2). [c] $p < 0.05$ versus slow cooling + CPG group (group 4).

CPG = St. Thomas cardioplegic solution; dP/dT = first derivative of left ventricular pressure; LVDP = left ventricular developed pressure; LVEDP = left ventricular end-diastolic pressure.

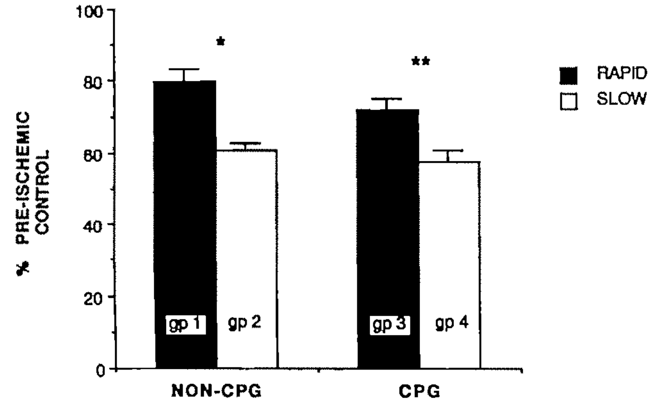

*Fig 3. Isovolumic left ventricular developed pressure postischemic recovery. Results are expressed as percent mean ± standard error of the mean of preischemic levels. Group 1 = rapid cooling alone (non-CPG), group 2 = slow cooling alone (non-CPG), group 3 = rapid cooling + CPG, and group 4 = rapid cooling + CPG. (CPG = cardioplegia; *p < 0.001, group 1 versus group 2; **p < 0.01, group 3 versus group 4.)*

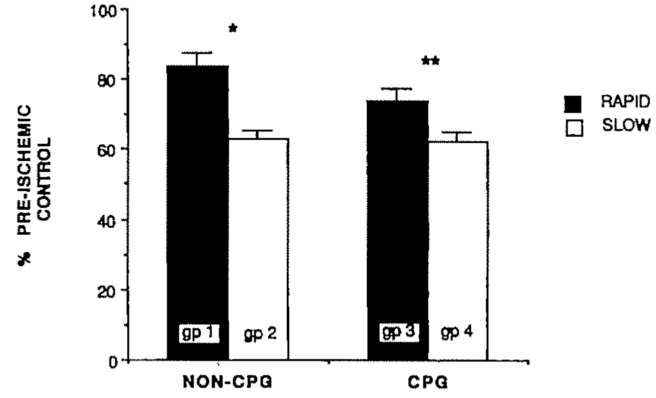

*Fig 5. Isovolumic negative first derivative of developed pressure recovery, expressed as mean ± standard error of the mean. (For groups, see Figure 3.) (*p < 0.01, group 1 versus group 2; **p < 0.05, group 3 versus group 4.)*

significant) (Fig 4). Corresponding values for recovery of −dP/dt were 84% ± 4% versus 63% ± 2% ($p < 0.01$) and 74% ± 4% versus 62% ± 3% ($p < 0.05$) (Fig 5).

Postischemic rise in LVEDP (Fig 6) was significantly less with rapid cooling as compared with slow cooling in the absence of cardioplegia (8% ± 5% versus 33% ± 7%; $p < 0.05$). Interestingly, the infusion of cardioplegia produced an increase in LVEDP in both group 3 (36% ± 12%) and group 4 (33% ± 18%). It is noteworthy that the addition of cardioplegia did not significantly improve functional recovery as compared with cooling alone. Heart rate was not significantly affected by the different modes of protection.

BIOCHEMICAL DATA. Myocardial ATP content values are shown in Figure 7. Baseline levels of ATP were similar in the rapid and slow cooling groups. Twenty minutes of slow cooling caused a significant decline in ATP levels from control (5.5 ± 0.2 versus 4.4 ± 0.3 $\mu g/g$; $p < 0.05$).

On the other hand, ATP levels were preserved after 5 minutes of rapid cooling. Between groups there was a significant difference in ATP levels at the end of the cooling periods: 6.0 ± 0.7 $\mu g/g$ with rapid cooling versus 4.4 ± 0.3 $\mu g/g$ at the end of slow cooling ($p < 0.05$). After 30 minutes of reperfusion, there was no recovery of ATP in either group. Furthermore, postreperfusion ATP levels were significantly less in group 2 as compared with group 1 (3.3 ± 0.2 versus 4.0 ± 0.1 $\mu g/g$; $p < 0.05$). Thus, there was a greater preservation of myocardial ATP after ischemia with prearrest rapid cooling. Creatinine phosphate levels demonstrated a similar decline with slow cooling as compared with rapid cooling. After reperfusion, CP levels were significantly less in group 2 versus group 1 (4.0 ± 0.2 versus 5.2 ± 0.3 $\mu g/g$; $p < 0.05$).

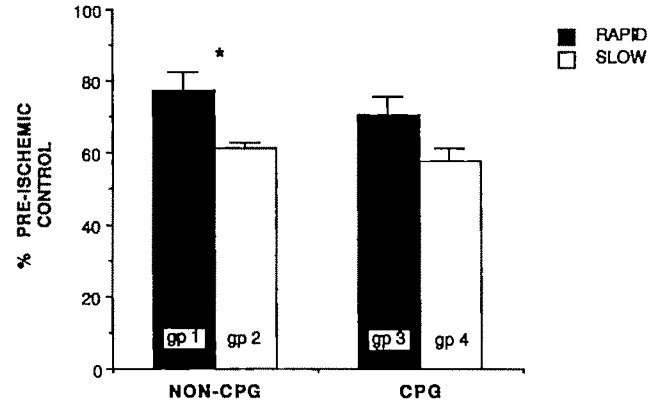

*Fig 4. Isovolumic positive derivative of developed pressure recovery, expressed as mean ± standard error of the mean. (For groups, see Figure 3.) (*p < 0.01, group 1 versus group 2.)*

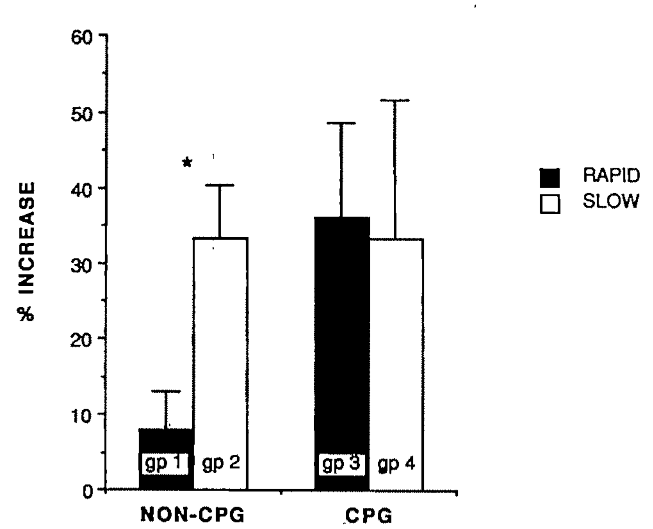

*Fig 6. Isovolumic postischemic rise in left ventricular end-diastolic pressure, expressed as mean ± standard error of the mean. (For groups, see Figure 3.) (*p < 0.05, group 1 versus group 2.)*

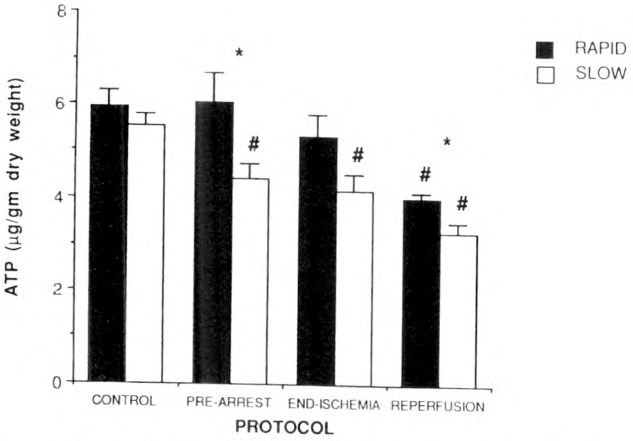

*Fig 7. Myocardial adenosine triphosphate (ATP) content (μg/g dry weight) at control, after rapid versus slow cooling (prearrest), at end of ischemia, and after reperfusion, expressed as mean ± standard error of the mean. (*p < 0.05, between-group difference; #p < 0.05, difference from control within group.)*

Rate Versus Duration of Cooling

VENTRICULAR FUNCTION. Data on the postischemic recovery of functional variables in the three study groups are presented in Table 3.

Postischemic recovery of LVDP (Fig 8) was significantly greater in group 1 as compared with groups 2 or 3 (80% ± 3% versus 64% ± 5% or 61% ± 2%; $p < 0.05$). Results for +dP/dt and −dP/dt demonstrated significantly greater levels with rapid cooling as compared with rapid cooling plus cold perfusion or slow cooling. Thus, after 30 minutes of reperfusion +dP/dt levels (Fig 9) were 77% ± 5% in group 1 versus 60% ± 4% in group 2 or 61% ± 1% in group 3 ($p < 0.05$). Corresponding postischemic values for −dP/dt (Fig 10) were 84% ± 4% versus 63% ± 6% or 63% ± 2% ($p < 0.05$). Postischemic rise in LVEDP (Fig 11) was significantly less with rapid cooling (8% ± 5%) as compared with group 2 or 3 (43% ± 14% or 33% ± 7%) ($p < 0.05$). Interestingly, after the respective cooling periods, the increase in LVEDP was significantly greater in group 2 (10 ± 0.5 mm Hg) and group 3 (10.4 ± 0.6 mm Hg) versus group 1 (4 ± 0.2 mm Hg) ($p < 0.05$).

BIOCHEMICAL DATA. Creatine phosphate values from serial right ventricular biopsies are presented in Table 4. Baseline levels were similar in all three groups. At the end of the cooling periods, CP levels were significantly reduced from preischemic levels in group 2 (4.5 ± 2 versus 5.7 ± 0.2 μg/g; $p < 0.05$) and group 3 (4.9 ± 0.3 versus 6.0 ± 0.2 μg/g; $p < 0.05$). Furthermore, there was a significant difference between groups at the end of the cooling period, with a greater preservation of CP levels in group 1 as compared with group 2 or group 3 (5.7 ± 0.3 versus 4.5 ± 0.2 or 4.9 ± 0.3 μg/g; $p < 0.05$). The latter difference was also seen at the end of 30 minutes of reperfusion with no recovery of CP in either group (4.6 ± 0.2 versus 3.8 ± 0.2 or 3.8 ± 0.1 μg/g; $p < 0.05$).

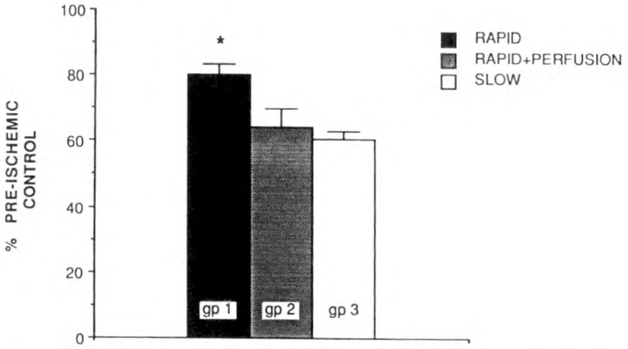

*Fig 8. Isovolumic postischemic recovery of left ventricular developed pressure, expressed as mean ± standard error of the mean. (Group 1 = 5 minutes of rapid cooling; group 2 = rapid cooling + 15 minutes of cold perfusion at 15°C; group 3 = 20 minutes of slow cooling.) (*p < 0.05, group 1 versus group 2 or group 3.)*

Comment

Protection of the myocardium during ischemia is an important objective of cardiac surgeons undertaking reparative operations for congenital heart disease in infancy. The complexity of operations in addition to the ever-decreasing age of patients has prompted investigators to optimize techniques to protect the immature heart.

Hypothermia has long been recognized to reduce the severity of ischemic damage of the heart, and it has become an essential component of myocardial protection [1–3]. Deep hypothermic circulatory arrest is a widely used method of protection in pediatric cardiac surgery. This technique usually involves exposing the heart to a period of cold perfusion on bypass as systemic core temperature is lowered, after which circulatory arrest is induced.

It has recently been suggested both from clinical experience [4] and experimental data [5] that rapid core cooling before the induction of cardiac arrest may induce myocar-

Table 3. Comparison of Ventricular Function With Rapid Cooling, Rapid Cooling + Cold Perfusion, and Slow Cooling[a]

Group	LVDP	+dP/dt	−dP/dt	LVEDP
1. Rapid cooling	80 ± 3[b]	77 ± 5[b]	84 ± 4[b]	8 ± 5[b]
2. Rapid + cold perfusion	64 ± 5	60 ± 4	63 ± 6	43 ± 14
3. Slow cooling	61 ± 2	61 ± 1	63 ± 2	33 ± 7

[a] All data expressed as percent mean ± standard error of the mean. [b] $p < 0.05$, group 1 versus group 2 or group 3.

dP/dt = first derivative of left ventricular pressure; LVDP = left ventricular developed pressure; LVEDP = left ventricular end-diastolic pressure.

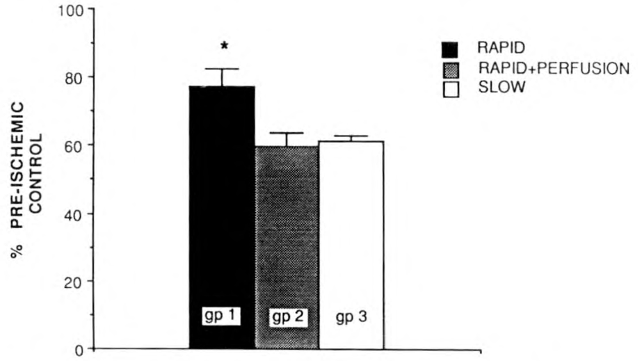

Fig 9. Isovolumic postischemic recovery of the positive first derivative of left ventricular pressure, expressed as mean ± standard error of the mean. (For groups, see Figure 8.) ($^*p < 0.05$, group 1 versus group 2 or group 3.)

dial contracture of the immature heart. It was postulated that this detrimental effect is due to increased levels of intracellular calcium with resulting contracture. Williams, Rebeyka, and their associates [4, 5] have since recommended the avoidance of rapid myocardial cooling before the induction of cardioplegic ischemic arrest.

The results of the present study suggest that rapid cooling is not detrimental to the ischemic neonatal myocardium when compared with slow cooling. Furthermore, and more importantly, prolongation of the rapid cooling period with additional perfusion produced a deterioration of ventricular recovery after ischemia.

Postischemic recovery of ventricular variables (LVDP, +dP/dt, −dP/dt) was significantly greater with 5 minutes of rapid cooling to 15°C as compared with slow cooling over 20 minutes. In addition, diastolic compliance showed significant deterioration with a marked elevation of LVEDP in the slow cooling group. Biochemical results correlated directly with the functional deterioration observed with slow cooling. Myocardial ATP levels were markedly reduced immediately after 20 minutes of slow cooling as compared with rapid cooling. Furthermore, the present study adds evidence to a growing body of literature suggesting that in a number of species, currently formulated cardioplegic solutions do not afford any greater protection than hypothermia alone in the immature heart [11, 12]. We were unable to demonstrate any beneficial effect of St. Thomas solution over hypothermia alone.

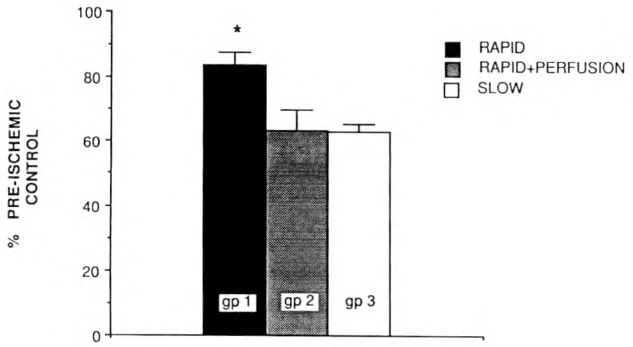

Fig 10. Isovolumic postischemic recovery of the negative first derivative of left ventricular pressure, expressed as mean ± standard error of the mean. (For groups, see Figure 8.) ($^*p < 0.05$, group 1 versus group 2 or group 3.)

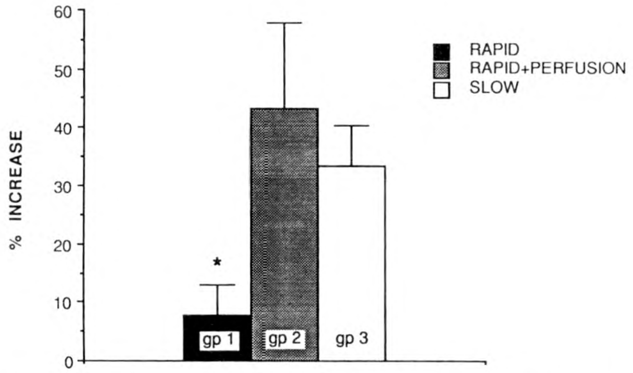

Fig 11. Isovolumic postischemic rise in left ventricular end-diastolic pressure, expressed as mean ± standard error of the mean. (For groups, see Figure 8.) ($^*p < 0.05$, group 1 versus group 2 or group 3.)

At first glance our study appears to be inconsistent with the findings of Rebeyka and associates [5], who suggest that rapid cooling before the induction of ischemic arrest produces marked deterioration in both ventricular function and myocardial energy stores. It should be noted that their findings were based on experiments performed on adult rabbits and not on newborn animals. Furthermore, closer scrutiny of their study groups reveals that the rapid cooling group was actually a combination of 5 minutes of rapid cooling from 37°C to 15°C and an additional period of cold perfusion at 15°C. We postulated, therefore, that the adverse effects of cooling as observed by Rebeyka and associates may in fact be due to a prolonged duration of prearrest hypothermic perfusion rather than a rapid rate of cooling. Our second series of experiments was designed to test this hypothesis. The data from these experiments demonstrated that postischemic diastolic and systolic ventricular indices were significantly greater with rapid cooling alone as compared with rapid cooling plus additional cold perfusion. In fact, there was no difference in recovery between slow cooling and the latter group. Myocardial CP levels were better preserved with rapid cooling alone, and further cold perfusion produced a significant decline in CP values both at the end of cooling and reperfusion.

Thus, our studies suggest that before the induction of arrest, adverse effects of hypothermic perfusion are duration dependent, and prolonged prearrest cooling is detrimental to the newborn heart. Furthermore, our data are indeed consistent with those of Rebeyka and associates, who show similar adverse effects of rapid cooling followed by cold perfusion as compared with normothermic perfusion before the induction of arrest. The confusion may be due in part to inappropriate representation of different cooling groups with respect to the rate of cooling and the total duration of hypothermic perfusion.

It is not easy to elucidate the mechanism by which

Table 4. Comparison of Myocardial Creatine Phosphate Levels With Rapid Cooling, Rapid Cooling + Cold Perfusion, and Slow Cooling[a]

Group	Control	End-Cooling	End-Ischemia	Reperfusion
1. Rapid cooling	5.9 ± 0.3	5.7 ± 0.3[b]	4.9 ± 0.3	4.6 ± 0.2[b]
2. Rapid + cold perfusion	5.7 ± 0.2	4.5 ± 0.2[c]	4 ± 0.2[c]	3.8 ± 0.2[c]
3. Slow cooling	6.0 ± 0.2	4.9 ± 0.3[c]	4.2 ± 0.2[c]	3.8 ± 0.1[c]

[a] All data expressed as mean ± standard error of the mean in micrograms per gram of dry weight. [b] $p < 0.05$, group 1 versus group 2 or group 3. [c] $p < 0.05$, difference from control levels within group.

prolonged hypothermia is detrimental to the newborn myocardium. It is known that cellular membranes undergo a phase transition as the temperature is reduced [13–15]. The phase transition of mammalian heart sarcolemma and mitochondrial membranes occurs in the range of 22° to 32°C [15, 16]. Therefore, it is tempting to speculate that as a result of these temperature-dependent transitions, a wide variety of membrane-associated functions are affected. These functions include mitochondrial calcium handling, calcium transport, and ATP-generating capacity. The biochemical results in our study depict a significant fall in ATP and CP content immediately after 20 minutes of slow or prolonged rapid cooling, but it is difficult to predict whether this in itself represents serious myocardial injury. Nordobeck and co-workers [17] similarly reported that cooling before arrest resulted in a rise in the ATP depletion rate. It is well known, however, that ATP is required for the maintenance of intracellular homeostasis of calcium and hence for the maintenance of low cytosolic calcium [18–20]. Consequently, depletion of tissue stores of ATP and CP might result in failure of ATP-dependent sequestration of calcium by the sarcoplasmic reticulum and the expulsion of calcium to the extracellular space. Under these circumstances a rise in cytosolic calcium could activate various membrane-located phospholipases and proteases, resulting in partial cell membrane damage and sudden influx of calcium into the cell with further deleterious effects. Thus, it is conceivable that cytosolic calcium loading during hypothermic perfusion may have detrimental effects during ischemic arrest.

Hypothermia has repeatedly been demonstrated to induce a positive inotropic response [21–23]. In our studies, diastolic compliance was affected to the same degree by both rapid and slow cooling, with an increase in end-diastolic pressure immediately after hypothermic perfusion. The inotropic effect of hypothermia has been shown to correlate with elevated levels of free cytosolic calcium in the myofibrillar region [24]. Shattock and Bers [25] have suggested that the positive inotropic response to hypothermia is not affected by sarcoplasmic reticular calcium availability. Bridge [26], however, has suggested the contrary. Although the mechanisms involved with calcium homeostasis have not been fully elucidated, there are differences in the handling of intracellular calcium flux between immature and mature hearts. Immature hearts are primarily dependent on extracellular rather than sarcoplasmic reticular calcium for control of cytosolic calcium [27], and thus it is conceivable that the inotropic effect of hypothermic perfusion in the immature heart may be due to the loss of integrity of the cell membrane.

In conclusion, our data demonstrate that the adverse effects of prearrest hypothermia are dependent on the duration of perfusion rather than the rate of cooling. We suggest that prolonged hypothermic perfusion before arrest is harmful to the newborn myocardium and should be avoided in pediatric cardiac surgery. As for the mechanism of the deleterious effect of hypothermia, we postulate that membrane-mediated changes occur, inhibiting a variety of functions including ATP generation and thus altering calcium homeostasis with consequent cellular damage and poor recovery of function.

We thank the Quebec Heart Foundation for their generous support.

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Flow Cytometric Analysis of Organ Preservation-Induced Endothelial Cell Membrane Damage

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Organ preservation for transplantation is associated with endothelial cell damage. This vascular injury results in increased capillary permeability, graft edema, and early graft dysfunction. This damage may be the limiting factor in preservation of these organs. This study uses flow cytometric assessment of membrane integrity to examine the effects of various organ preservation solutions on human umbilical vein endothelial cell cultures. Confluent plates of human umbilical vein endothelial cells were incubated at 4°C for 24, 48, and 72 hours in commonly used preservation solutions. After cold incubation, the cells were harvested and stained with propridium iodide and fluorescein diacetate. Cells were examined using a flow cytometer for membrane integrity and cytosolic activity. When examined after 24, 48, and 72 hours, cells stored at 4°C in a 5% polyethylene glycol salt solution were significantly less damaged than those stored in any other solution ($p < 0.05$). After 48 and 72 hours at 4°C, cells stored in ViaSpan were significantly more intact than cells stored in EuroCollins and 0.9% saline solution ($p < 0.05$). This study demonstrates that endothelial cell damage occurs during cold storage and that a polyethylene glycol–based solution showed superior cellular preservation.

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The development of organ preservation techniques has allowed the widespread clinical application of transplantation. Graft preservation using current procedures is clearly not ideal. Improved methods of organ preservation would result in improved clinical results, as well as more widespread organ sharing. Organ preservation is particularly critical in lung preservation, and much of the early lung dysfunction seen after transplantation is attributed to preservation injury. The sensitivity of the lung to preservation injury currently limits the ischemic time to less than 6 hours.

Investigations into improved solutions for organ preservation have been hampered by the expense, time, and facility requirements associated with animal research. The development of tissue culture models for transplanted organs would result in more widespread testing of new solutions and techniques. This study investigates the use of human umbilical vein endothelial cells as a model for organ storage.

The determination of cellular viability after exposure to hypothermic storage solutions can be problematic. This study makes use of a technique proposed for the assessment of effects of chemotherapeutic drugs on tumor cell lines. The flow cytometer is a rapid automated cell sorting device using laser light to differentiate cell populations. The flow cytometer was used to determine cellular viability based on the reactions of the endothelial cells to propridium iodide (PI) and fluorescein diacetate (FDA). These stains provide separate but complementary information: the FDA stains only live cells green and the PI stains only dead cells red [1].

Reports concerning the use of this technique on tumor cell lines have shown excellent correlation between viability as determined by the flow cytometer and subsequent demonstrations of cell growth in culture [1]. This study uses the flow cytometer and the combination staining technique described above to assess the cytotoxicity of organ preservation solutions at 4°C on human umbilical vein endothelial cells.

Material and Methods

All cell culture reagents were obtained through the tissue culture facility of the Lineberger Cancer Research Center, University of North Carolina at Chapel Hill. Cells were harvested from umbilical cords using techniques described previously [2]. In brief, umbilical cords were obtained from recent deliveries and placed in a holding solution of Hanks' balanced salts, antibiotics (PSF: penicillin sodium, 100 IU/mL; streptomycin sulfate, 100 μg/mL; and amphotericin B, 2 μg/mL), and 10,000 U/L heparin. Cords were stored at 4°C until cells could be harvested, usually in less than 4 hours. At the time of the harvest, the umbilical vein was cannulated and flushed with lactated Ringer's solution until grossly clear of red blood cells. The vein was then distended with 0.1% collagenase type 1A (C-9891; Sigma Chemical Co, St. Louis, MO) and incubated at 37°C for 10 minutes. The collagenase solution containing the endothelial cells was drained into a sterile centrifuge tube. The vein was flushed twice with 15 mL of media 199 and the effluent was collected, added to the cells, and centrifuged at 1,000 *g* for 10 minutes. The supernatant was discarded and the pellet of

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endothelial cells was suspended in 15 mL of media 199 containing 10 mmol/L of HEPES, 15 mg of endothelial cell growth supplement (40006; Collaborative Research Inc, Bedford, MA), 1 mmol/L sodium pyruvate, 16% pooled human serum, and antibiotics (PSF). Cells and media were transferred to 0.1% gelatin-coated (Sigma G-1319) T-75 flasks. Cells were refed after 24 hours and every 2 or 3 days thereafter. Identification of endothelial cells was confirmed by morphology, by characteristic contact growth inhibition, and by fluorescent label monoclonal antibody staining to factor VIII. Cells grew to confluence in 3 to 4 days and were passed by application of trypsin (0.05% trypsin–0.02% EDTA) to the monolayer and reseeding of the cells into gelatin-coated 12-well plates. All experiments were conducted on confluent monolayers of second passage primary cells. Each experimental and control group was obtained from a single umbilical cord.

Solutions tested included ViaSpan (VIA) (Belzer UW; Du Pont Pharmaceuticals, Wilmington, DE) EuroCollins (EC) (Baxter Healthcare Corp, Pharmacy Division, Deerfield, IL) 0.9% saline solution (NS) (Baxter), and a 5% solution of polyethylene glycol (Sigma P-2263; molecular weight, 15,000 to 20,000) in Hanks' balanced salts solution (PEG) supplemented with minimum essential medium essential amino acids (320-1130AG-50X; Gibco Research Products, Grand Island, NY) and minimum essential medium nonessential amino acids (Gibco 320-1140AG-100X). The pH was adjusted to between 7.2 and 7.4. The composition of the solutions are shown in Table 1. Control cells were kept at 37°C in media 199 supplement as described (warm media). Test solutions were applied to confluent monolayers, and plates were incubated at 4°C for 24, 48, and 72 hours. The plates were then removed, the monolayer was lifted by applying 300 μL of 0.05% trypsin–0.02% EDTA, and the plates were incubated for 5 minutes at 37°C. The trypsin was then inactivated by application of 100 μL of fetal calf serum and 200 μL of phenol red free DMEM/F-12. The stains used were FDA (Sigma F-7378) and PI (Sigma P-4170). A stock solution of PI, 500 μg/mL in Hanks' balanced salts solution, was prepared and stored at 4°C. A stock solution of FDA was prepared by dissolving the FDA in acetone to form a solution of 1,000 μg/mL. The acetone-FDA solution was stored at 4°C and was stable for several weeks under these conditions. The day of the experiment, the FDA stock was diluted to 0.2 μg/mL in Hanks' balanced salts solution, and the PI solution was diluted to a concentration of 250 μg/mL. The cells and stains were transported to the cytometry facility on ice.

Table 1. Components of Preservation Solutions[a]

Components	EuroCollins	ViaSpan (UW)	0.9% Saline	HBSS-PEG
Na^+	9.3	28	145	137.68
K^+	108	125	. . .	5.8
Mg^{2+}	. . .	5	. . .	0.4
Cl^-	14	. . .	145	144.92
HCO_3^-	9.3	. . .	. . .	. . .
SO_4^-	. . .	5	. . .	0.4
PO_4^{-3}	93	25	. . .	0.74
Ca^{2+}	. . .	. . .	. . .	1.26
D-Glucose	182	. . .	. . .	5.5
Raffinose	. . .	30	. . .	. . .
Lactobionate	. . .	100	. . .	. . .
Allopurinol	. . .	1	. . .	. . .
Glutathione	. . .	3	. . .	. . .
Adenosine	. . .	5	. . .	. . .
Pentafraction (g/L)	. . .	50	. . .	. . .
PEG	. . .	. . .	. . .	2.78
moSm/L	310–320	310–320	310–320	310–320
pH	7.2–7.4	7.4	5	7.2–7.4
MEM amino acids	. . .	. . .	. . .	2 mL
MEM nonessential amino acids	. . .	. . .	. . .	1 mL

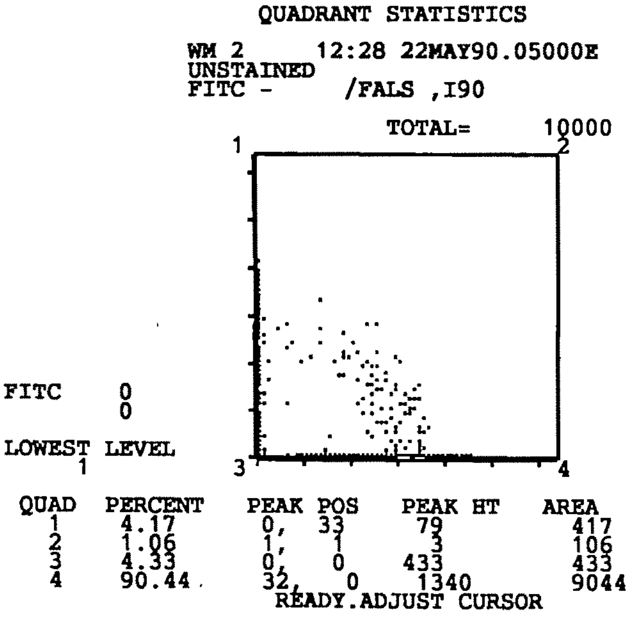
[a] Values are given in mmol/L unless otherwise indicated.

HBSS-PEG = Hanks' balanced salts with 5% polyethylene glycol; MEM = minimum essential medium Eagle additives; PEG = polyethylene glycol (Sigma P-2263).

Five hundred microliters of cell suspension was stained by the addition of 100 μL of the FDA dye and 100 μL of the PI dye, and the cells were allowed to react for 3 minutes. The cells were then examined using a Coulter EPICS 752A flow cytometer (Coulter Scientific Electronics Instruments Inc, Hialeah, FL). The argon laser was used at a wavelength of 488 nm to excite samples. The signal was split using a 550-nm long pass dichroic mirror. The signal was gated on 90-degree light scatter versus log forward angle light scatter. A 650-nm long pass filter was used for cells stained with PI, and a 525-nm band pass filter was used for cells stained with FDA. Quadrant analysis was performed with cells staining high green, no red counted as viable, cells staining no green, high red counted as dead, and cells staining both green and red counted as membrane damage (Fig 1). Ten thousand cells were counted for each well, and counts were performed in triplicate for each trial. A total of three trials were performed, and the results were combined and analyzed using two-way analysis of variance. Values of p less than 0.05 were considered significant.

Results

Results are reported as mean percentage viable cells per well (high green staining) ± standard error. The viability of control cells kept in media and at 37°C was greater than 85% at all time periods. After 24 hours of exposure to 4°C, cell populations stored in PEG solutions displayed significantly higher viability than cells stored in VIA, EC, or NS ($p < 0.001$). Viability for PEG cells was 83% ± 3.5%, compared with 73% ± 5.9% for VIA; 71% ± 5.7% for EC, and 68% ± 7.3% for NS. ViaSpan was not significantly superior to EC at 24 hours ($p = 0.882$). At 48 hours, PEG (81% ± 2.9%) was again significantly better than VIA (61% ± 8.7%) ($p < 0.001$). Cells stored in VIA were significantly better than those stored in either EC (51% ± 11.3%) or NS (53% ± 7.4%) ($p = 0.01$). After storage for 72



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                  QUADRANT STATISTICS
            WM 2      12:28 22MAY90.05000E
            UNSTAINED
            FITC -      /FALS ,I90
                               TOTAL=      10000
                  1                            2

FITC       0
           0

LOWEST  LEVEL
     1            3                            4

QUAD    PERCENT    PEAK POS     PEAK HT     AREA
  1       4.17      0,   33        79         417
  2       1.06      1,    1         3         106
  3       4.33      0,    0       433         433
  4      90.44     32,    0      1340        9044
                     READY.ADJUST CURSOR
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Fig 1. A representative quadrant analysis of warm media cells by the flow cytometer. Quadrant (QUAD) 1 represents the percentage of dead (high red staining) cells, quadrant 2 the percentage of damaged cells (both red and green staining) cells, quadrant 3 the percentage of debris, and quadrant 4 the percentage of viable (high green staining) cells.

hours, PEG continued to provide the best cellular preservation, with 76% ± 5.1% of cells being viable compared with 60% ± 11.3% for VIA ($p < 0.001$). ViaSpan also remained superior to both EC (42% ± 10.9%) and NS (45% ± 10.6%) ($p < 0.001$) (Fig 2).

When red stained (dead) or red and green (damaged) cells were examined, a similar pattern was observed. These results are reported as mean percentage of the sum dead (high red stained) plus damaged cells (both red and green stained) per well ± standard error. At 24 hours, mean percentage of dead plus damaged cells in the warm media control group was 8.6% ± 1.5%; for PEG, 11.1% ± 3.5%; VIA, 20.4% ± 5.8%; EC, 21.8% ± 5.5%; and NS, 23.7% ± 6.9% ($p > 0.05$). After 48 hours, cells stored in PEG displayed significantly less damage than cells stored in VIA, EC, and NS ($p < 0.05$). Dead plus damaged cell percentages were as follows: warm media, 7.1% ± 0.6%; PEG, 12.0% ± 2.5%; VIA, 29.5% ± 7.3%; EC, 29.6% ± 5.5%; and NS, 36.5% ± 6.7%. After 72 hours, PEG-stored cells were again significantly less damaged than cells stored in VIA, EC, and NS ($p < 0.05$). Dead plus damaged cell percentages were as follows: warm media, 9.7% ± 2.4%; PEG, 16.9% ± 4.3%; VIA, 31.9% ± 9.2%; EC, 30.0% ± 4.0%; and NS, 44.8% ± 9.2% (Fig 3).

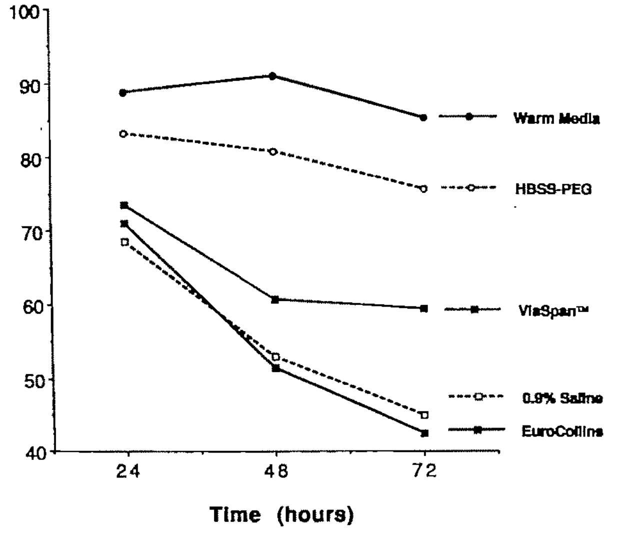

Fig 2. Percent human umbilical vein endothelial cells viable as assessed by flow cytometry versus time (hours) after storage at 4°C. (HBSS-PEG = Hanks' balanced salts with 5% polyethylene glycol.)

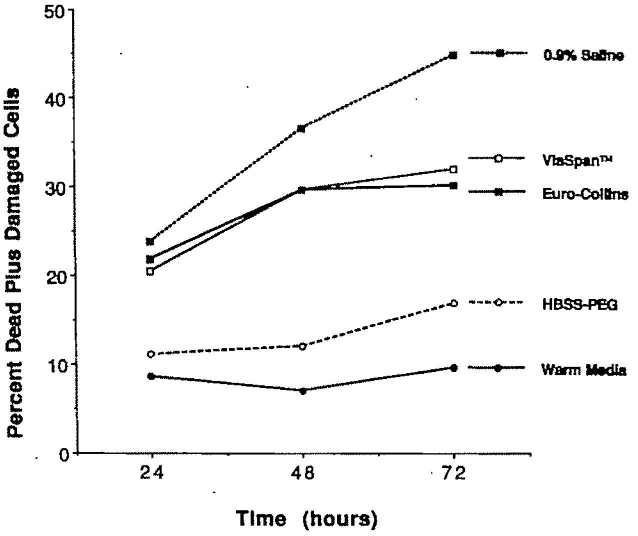

Fig 3. Percent human umbilical vein endothelial cells dead plus damaged as assessed by flow cytometry versus time (hours) after storage at 4°C. (HBSS-PEG = Hanks' balanced salts with 5% polyethylene glycol.)

Comment

The development of new immunosuppressive drugs and improved technology have resulted in a dramatic increase in organ transplantation over the past decade. With this increased demand, the preservation of organs has become of major concern. The most widely used solution for organ preservation was developed by Collins in the 1960s, and little improvement in this intracellular electrolyte-based solution was made for nearly 20 years. EuroCollins solution allowed for the preservation of kidneys for up to 48 hours and allowed for the development of regional networks for organ sharing and tissue matching for renal transplantation. The availability of liver transplantation generated renewed interest in the problem of organ preservation, because EC provided only limited storage time for harvested livers. In the mid-1980s, Belzer developed a new solution containing reduced glutathione, lactobionate, and hydroxyethyl starch which significantly prolonged the safe storage time for liver grafts and enabled widespread organ sharing, more precise tissue and size matching, and reduced preservation-associated organ dysfunction.

Research concerning organ preservation has been conducted primarily in whole organ models. There are several disadvantages to the use of animal models, including the necessity for a veterinary facility, high cost, and the length of time required to allow an animal to recover from operation and reach an endpoint. In addition, increasing interest in the development of alternatives to animal models has been prompted by animal welfare activists.

Several studies have been published using a tissue culture model to test hypothermic preservation [3–5]. Most of these studies involve the application of preservation solutions to cultured animal cells, including rat hepatocytes, rat alveolar type II cells, and rabbit renal tubular cells. The predominant cell type for the organ of interest is often selected for study.

The endothelial cell is ubiquitous in transplanted organs. Lining the vascular tree, the endothelial cell is the interface between graft and host tissue. The endothelium is also the only tissue that is in direct contact with the preservation solution. Endothelial cell damage has been implicated in graft failure in liver transplantation. In lung transplantation, damage to the endothelial cell barrier resulting in interstitial edema appears to be a critical limiting factor in prolonged lung preservation [6].

The study of hypothermic preservation solutions in vitro using human endothelial cells has been limited by the lack of reported techniques for the assessment of cytotoxicity using this cell line. A variety of techniques are available for the assessment of cytotoxicity in general, including clonogenic assays, metabolic tests, and membrane exclusion tests. This study makes use of the flow cytometer, a device that uses laser light to determine cell color, size, and count cells. It is an automated assay capable of counting 10,000 cells in less than a minute. Trigger criteria are operator programmable. Large sample sizes can be examined, resulting in a very low sampling error.

Fluorescein diacetate is a minimally fluorescent, nonpolar molecule that is rapidly taken through the cell membrane into the cytoplasm. Inside the viable cell, nonspecific cytoplasmic esterases cleave the diacetate moiety, forming fluorescein. Fluorescein is both highly fluorescent and polar and cannot escape from the cells with intact cellular membranes. Live cells containing fluorescein molecules fluoresce bright green under ultraviolet laser light. Propridium iodide is a polar molecule with a high affinity to chromatin. It cannot enter a cell with an intact cellular membrane [7]. The use of two different stains, one staining only live cells and one staining only dead cells, provides a unique method of assuring the accuracy of measurements. The live cells and dead cells are counted by the flow cytometer independently. The information obtained from the flow cytometer display includes the number of cells staining both red and green as well as an indication of the amount of cellular debris present in the preparation. Higher amounts of debris were seen in trials with large numbers of dead cells, which is consistent with other reports [8]. Cells containing both red and green dye were observed both by the flow cytometer and under direct vision using fluorescent microscopy. These cells have sustained sufficient membrane damage to allow entry of PI but have not yet lysed. Hence, these cells were classified as membrane damaged.

In this study, the highest cellular viability was seen with cells stored in a phosphate-buffered saline solution containing 5% PEG. This solution surpassed the clinically used preservation solutions, ViaSpan (Belzer UW) and EuroCollins, at all time intervals. After 24 hours, cellular viability for cells stored in PEG was not statistically different from controls stored in 37°C tissue culture media. Although the use of PEG as an additive to preservation solution is unorthodox, several studies have suggested it may be beneficial [3, 4, 9]. The mechanism of cryoprotection afforded by PEG is not well understood. It has been suggested that increased viability may be in part due to stearic hindrance by the PEG molecule, which serves to isolate the cellular membrane from other solvents [10]. This insulation may prevent membrane damage from swelling caused by unrestricted ion passage in the presence of a nonfunctional sodium-potassium adenosine triphosphatase pump during cold storage. The effect is clearly not simply an osmotic action, because equal osmolar concentrations of other large impermeants such as mannitol, dextran, and raffinose do not afford the same protection as PEG. Mack and associates [11] have reported inhibition of lipid peroxidation with addition of PEG to hepatocytes in culture, suggesting that a further action may be protection of the cellular membrane from superoxide-induced damage. Human umbilical vein endothelial cells stored in PEG-based solution at 4°C have shown increased viability when assayed for metabolic activity as measured by 3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide (Sigma M2128) reduction (Killinger WA, Dorofi DB, Keagy BA, Johnson G; unpublished results). This suggests that the increase in survival noted using flow cytometry is not simply due to an artifactual sealing of the membranes of already dead cells.

Polyethylene glycol obtained from commercial suppliers has been reported to contain contaminating aldehydes, peroxides, and cytotoxic preservatives [9, 12]. Although we did not test specifically for the presence of any of these contaminants, our model failed to show any deleterious effects from exposure to the PEG solutions. The only processing the PEG underwent was a 15-minute autoclaving for sterilization.

The effects of PEG 20M compound on the kidney are not well characterized. Low molecular weight PEG and monomeric ethylene glycol can cause nephrotoxicity. In general, as the molecular weight of the PEG increases the toxic effects decrease [13]. Polyethylene glycol 20M has shown very low toxicity in several studies in laboratory animals [14]. This compound has been used in a whole organ transplant model in rats with no reported renal toxicity [15].

The significance of the umbilical vein endothelial cell model for organ preservation has not yet been established. Correlation using other established techniques including whole organ preparations is necessary to validate results obtained by any screening technique. This study presents a new technique for the assessment of endothelial cell viability and applies this technique to a model of hypothermic organ preservation. This procedure provides a rapid, automated, and highly accurate method for the screening of cytotoxic effects. It provides information concerning the effects of preservation on individual cells rather than on cell populations and may prove useful in the development of improved techniques for organ preservation.

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Platelet Protection by Aprotinin in Cardiopulmonary Bypass: Electron Microscopic Study

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To evaluate the functional integrity of platelets in patients administered the proteinase inhibitor aprotinin during cardiopulmonary bypass, 20 patients undergoing a complicated and prolonged open heart operation were studied. They were randomized to receive either a high dose of aprotinin (total dose, 6 to 7 × 10^6 KIU) before and during cardiopulmonary bypass (10 patients) or a placebo (10 patients). Blood samples were collected preoperatively, at the termination of bypass, and 90 minutes thereafter to assess platelet count and aggregation on extracellular matrix, which was studied by scanning electron microscopy. On a scale of 1 to 4, mean preoperative platelet aggregation grades were similar in both groups (3.5 ± 0.5). Postoperatively, at the termination of cardiopulmonary bypass and 90 minutes thereafter, all 10 patients treated with aprotinin revealed normal, unchanged platelet aggregation (grade, 3.5 ± 0.5), whereas all placebo-treated patients showed severely disturbed aggregation (grade, 1.4 ± 0.5) ($p < 0.001$). The platelet count was similar in both groups before and after operation (preoperatively, 182 ± 75 × 10^9/L and 146 ± 30 × 10^9/L, and postoperatively, 87 ± 13 × 10^9/L and 80 ± 27 × 10^9/L for the aprotinin and placebo groups, respectively). Total 24-hour postoperative bleeding and blood requirement were significantly lower in the aprotinin group (371 ± 84 mL and 2 ± 0.7 units, respectively) compared with the placebo group (608 ± 28 mL and 3.4 ± 1.3 units, respectively) ($p < 0.01$). These results demonstrate that improved postoperative hemostatis is directly related to the complete preservation of platelet function achieved by the protective properties of aprotinin.

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The impaired hemostatis observed after cardiac operations is mainly due to impaired platelet function [1–5]. Administration of the proteinase inhibitor aprotinin improves intraoperative and postoperative platelet function, thus reducing postoperative blood loss and blood requirements [6, 7]. In addition to inhibiting plasmin and kallikrein during cardiopulmonary bypass (CPB), aprotinin improves the hemostatic platelet function by preserving adhesive platelet membrane receptors (glycoprotein Ib) [8], thus preventing platelet activation during contact with perfusion systems.

In several previously published studies, we [9, 10] demonstrated that CPB causes a significant decrease in the ability of platelets to interact with the subendothelial layer. Using the extracellular matrix (ECM) model and the scanning electron microscope, it was shown in all patients that platelets in blood samples drawn at the end of CPB cannot form mature aggregates similar to those formed before CPB [9].

The purpose of this study is to evaluate with the ECM model the preservative effect of aprotinin on platelet function after CPB. To better evaluate the effect of aprotinin on blood loss, patients with potentially prolonged bypass times were selected for the study.

Material and Methods

After giving informed consent, 20 patients undergoing potentially prolonged CPB procedures were randomized to receive either a high dose of aprotinin before and during CPB (group 1, 10 patients) or a placebo (group 2, 10 patients) (Table 1). The study group (group 1) received a loading dose of 2 × 10^6 KIU of aprotinin (Trasylol; Bayer, Leverkusen, Germany) over 20 minutes before sternotomy, followed by continuous infusion of 0.5 × 10^6 KIU per hour until skin closure at the end of the operation. An additional 2 × 10^6 KIU was added to the priming volume of the oxygenator. Hence, each patient in the study group received a total dose of 6 to 7 × 10^6 KIU of aprotinin. Each patient in the control group (group 2) received equivalent volumes of the placebo solution (0.9% saline solution) at the respective times.

The mean age of the patients was 62 ± 9 years (range, 41 to 78 years), with no difference between the two groups. Preoperative hemoglobin levels were similar in both groups (see Table 1), and no patient had been receiving dipyridamole or aspirin-containing drugs during the 4 weeks preceding the operation. For all patients, a Sarns pump (Sarns Inc, Ann Arbor, MI) and bubble

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Table 1. Clinical and Operative Data[a]

Variable	Group 1 (Aprotinin) (n = 10)	Group 2 (Placebo) (n = 10)
Age (y)	58 ± 11	65 ± 7
Sex (male/female)	9/1	7/3
Hemoglobin level (g/100 mL)	13.2 ± 0.5	13.3 ± 0.4
Bypass time (min)	185 ± 32	167 ± 36
Aortic cross-clamp time (min)	63 ± 27	56 ± 35
Lowest body temperature (°C)	25 ± 2.6	25 ± 4.3
Procedure		
CABG	2	4
Redo CABG	3	2
Valve replacement	0	2
CABG + valve replacement	5	1
CABG + aneurysmectomy	0	1

[a] Where applicable, data are shown as the mean ± the standard deviation.

CABG = coronary artery bypass grafting.

oxygenator (Bentley Laboratories, Inc, Irvine, CA) were used. The oxygenators were primed with 1,500 mL of Hartmann's solution and 500 mL of 5% dextrose solution.

The two groups were similar with regard to bypass time, aortic cross-clamp time, and lowest body temperature (see Table 1). All patients were rewarmed to 35°C before discontinuation of CPB. Reversal of the effect of heparin sodium by protamine sulfate was monitored by the activated clotting time [11]. All pump blood was returned to the patient through the aortic cannula or intravenously from infusion bags without hemoconcentration. None of the patients had to be returned to the operating room because of excessive mediastinal bleeding.

Blood samples obtained through a flushed arterial catheter were collected from each patient at the following times: preoperatively (immediately after induction of anesthesia and before administration of heparin), at the termination of CPB, and 90 minutes thereafter. Platelet count was measured with a Coulter-Counter-S-Plus II (Luton, England).

Preparation of Dishes Coated With Extracellular Matrix

Corneal endothelial cells were grown on 12 well-type tissue culture plates (Nunc GmbH, Roskilde, Denmark) with 5% dextran T-40 (Pharmacia Fine Chemicals, Uppsala, Sweden) added to the growth medium as previously described [12]. Cultures were washed once with phosphate-buffered saline solution and exposed to 0.5% Triton-X 100 solution in phosphate-buffered saline solution (vol/vol), followed by exposure to ammonium hydroxide solution, 0.1 mol/L, and washing in phosphate-buffered saline solution. Extracellular matrix–coated dishes containing phosphate-buffered saline solution were stored before use at 4°C for up to 3 months.

Platelet Reactivity With Extracellular Matrix

Whole blood (0.5 mL in a citrate buffer) from each sample was added to the tissue culture well (16-mm diameter) coated with ECM and agitated (100 rpm) (Orbit Shaker; Lab-Line Instruments, Melrose Park, IL) for 30 minutes at room temperature. At the end of the incubation period, all blood from the culture dish was collected, and the dish was gently flushed several times with phosphate-buffered saline solution.

Preparation for Scanning Electron Microscopic Study

The ECM–coated dishes, now containing platelet aggregates, were fixed in 2.5% phosphate-buffered glutaraldehyde (pH 7.2), washed in the same buffer, and postfixed in 2% osmium tetroxide. The third fixation was in a solution of 2% tannic acid–guanidine hydrochloride. The triple-fixed samples were dehydrated in graded alcohol solutions, and thereafter the alcohol was exchanged for Freon 112 by graded Freon solutions (Du Pont Company, Wilmington, DE). The samples were air-dried, gold-coated, and examined by a Jeol 840 scanning electron microscope (Jeol USA Inc, Peabody, MA).

Grading Platelet Aggregates on Extracellular Matrix

As a method of quantitating the aggregation of platelets on ECM as seen by the scanning electron microscope, four distinct aggregation grades were defined according to the various platelet morphological types [9]: In grade 1, the platelets were discoid with a lentiform appearance, have a smooth surface, and lack any pseudopodia. The platelets do not adhere to each other, and each platelet can be seen individually. In grade 2, the platelets display the first signs of activation, and they appear with slender dendritelike pseudopodia, still separated from each other. In grade 3, the aggregation process is more advanced. The platelet body spreads, showing multiple dendritic pseudopodia, and the platelets start to cluster. In this immature aggregate, each platelet can still be identified separately. Grade 4 consists of a mature aggregate in which large clumps of platelets are seen and in which individual platelets are difficult to define.

In each sample, 40 scanning electron microscopic fields containing platelets were examined at a magnification of 8,000, and each was given an individual grade. The final aggregation grade of each sample was derived by calculating the arithmetic mean of the individual grades. Although aggregates of different grades could be found in any given sample, a dominant grade for each sample could always be identified. To avoid any element of subjectivity in the grading process, the observers assigned grades blindly, that is, they were not aware of the group to which each sample belonged while grading it.

The indication for homologous red blood cell transfusion was a hemoglobin level of less than 100 g/L (10 g/100 mL). Platelet transfusion in active bleeders (more than 200 mL/h in the first 2 postoperative hours) was given when the platelet count was lower than 100 × 10^9/L. Blood loss from the chest tubes, the number of blood units required, and the total number of blood products transfused (red blood cells, plasma, and platelet units) in the initial 24 hours after the patient arrived in the intensive care unit were recorded for evaluation of clinical hemostatis.

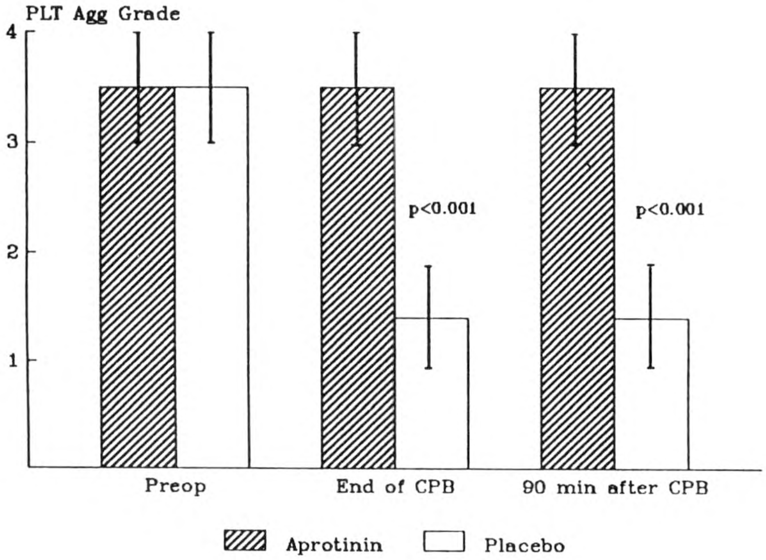


Fig 1. Comparison of platelet aggregation grades (PLT Agg Grade) on extracellular matrix in the two groups before operation, immediately after termination of cardiopulmonary bypass (CPB), and 90 minutes thereafter.

Statistical Analysis

Results were expressed as the mean ± the standard deviation. Paired and nonpaired *t* tests were used as applicable for statistical analysis.

Results

The preoperative platelet count in group 1 (aprotinin) (182 ± 75 × 10^9/L) did not differ significantly from that in group 2 (146 ± 30 × 10^9/L). Similarly both groups showed a significantly lower platelet count after CPB (87 ± 13 × 10^9/L, group 1, and 80 ± 27 × 10^9/L, group 2).

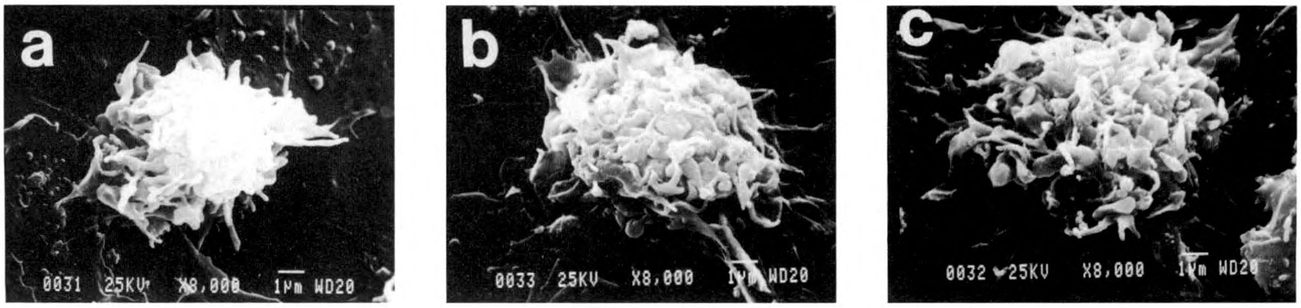
The mean preoperative grade of platelet aggregation was 3.5 ± 0.5 in both groups (Fig 1). At the end of CPB, no change in platelet aggregation grade was noted in any of the patients in the aprotinin group (mean grade, 3.5 ± 0.5) (Fig 2; see Fig 1), whereas in the placebo-treated group, all patients showed a significant decline to grade 1 or 2 (mean grade, 1.4 ± 0.5) ($p < 0.001$) (Fig 3; see Fig 1). This difference between the two groups remained in the measurements made 90 minutes after CPB (see Figs 1–3).

Total 24-hour blood loss in group 1 was significantly lower than that in group 2 (Table 2). Patients in the aprotinin-treated group received fewer homologous red blood cell units and were exposed to a smaller number of homologous blood products than patients in group 2, mainly because of the use of platelet units in 3 group 2 patients as compared with no group 1 patients (see Table 2). The 24-hour postoperative hemoglobin level was 126 ± 9 g/L (12.6 ± 0.9 g/100 mL) in group 1 and 124 ± 8 g/L (12.4 ± 0.8 g/100 mL) in group 2 (p = not significant).

Comment

Several recently published studies [6–8] have shown a significant platelet-protective effect of the proteinase inhibitor aprotinin from damage caused by contact with surfaces of the extracorporeal system. The improved platelet function and hemostatis observed were related to the protective effect of aprotinin on platelet membrane glycoprotein Ib, which is the adhesive receptor [8, 13], and glycoprotein IIb/IIIa, which is a membrane fibrinogen receptor related to aggregation [14–16].

In this study, the biochemical explanations for better platelet function in patients treated with aprotinin were strongly supported by scanning electron microscopic evidence of better platelet aggregability on the ECM. Cultured endothelial cells, which closely resemble their in


a
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0031 25KV X8,000 1μm WD20
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Fig 2. Scanning electron micrographs from patient who received aprotinin: (a) before operation (grade 4); (b) end of cardiopulmonary bypass (CPB) (grade 4); and (c) 90 minutes after CPB (grade 4). (× 8,000 before 21% reduction.)

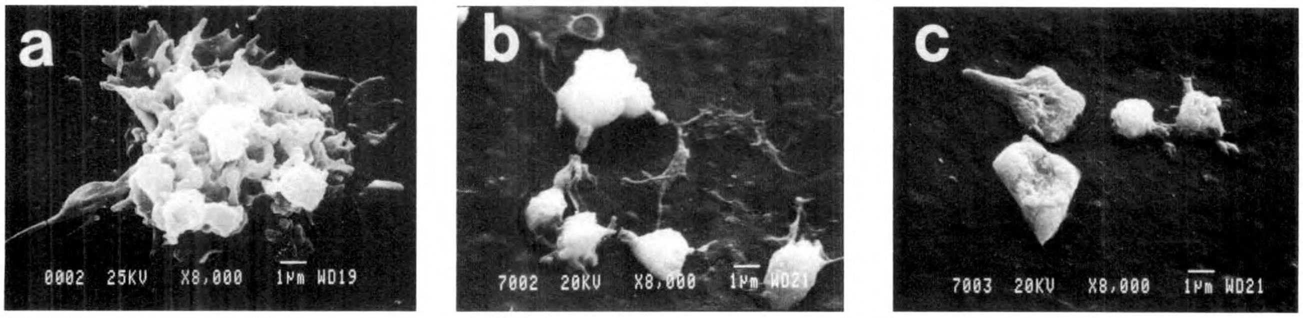
a
0002 25KV X8,000 1µm WD19
b
7002 20KV X8,000 1µm WD21
c
7003 20KV X8,000 1µm WD21

Fig 3. Scanning electron micrographs from patient who received placebo: (a) before operation (grade 4); (b) end of cardiopulmonary bypass (CPB) (grade 1); and (c) 90 minutes after CPB (grade 1). (× 8,000 before 21% reduction.)

vivo counterparts, produce an ECM, secreted exclusively beneath the cell layer. This ECM resembles the vascular subendothelial basal lamina in its organization and macromolecular constituents (fibronectin, laminin, collagens type III, IV, and V, and sulfated proteoglycans) [12, 17]. Denudation of the endothelial cell monolayer leaves the underlying ECM intact and firmly attached to the entire surface of the culture dish. The ECM prepared in this way retains its characteristic amorphous structure and biological properties [12, 17]. Several studies [18–21] have shown that the ECM produced either by bovine or human endothelial cells can serve as an excellent in vitro model for the study of platelet–subendothelium interaction.

Extracorporeal circulation caused a significant decrease in aggregation grade in all patients in the placebo group (mean aggregation grade after CPB was 1.4 compared with 3.5 before CPB). This deleterious effect of CPB did not appear in any of the 10 patients treated with aprotinin (mean aggregation grade after CPB was 3.5).

As platelet aggregation on ECM requires both fibrinogen [19] and the von Willebrand factor [22] as ligands for the activated glycoprotein IIb/IIIa, our model is not sensitive enough to differentiate which domain on the glycoprotein IIb/IIIa was protected by aprotinin. The preserved aggregatory capacity of platelets in the aprotinin group of our study demonstrates that at least part, if not all, of the glycoprotein IIb/IIIa was protected.

To evaluate the clinical importance of better postoperative hematological hemostasis, patients selected for this study were undergoing operation requiring a potentially prolonged period of CPB. Indeed, although the aprotinin group underwent more complicated procedures than the placebo group (see Table 1) and therefore had a more prolonged CPB time, aprotinin administration significantly reduced both postoperative blood loss and the need for transfusion of homologous red blood cells or other blood products.

Table 2. Postoperative Bleeding and Blood Requirements

Variable	Group 1 (Aprotinin)	Group 2 (Placebo)	*p* Value
24-Hour bleeding (mL)	371 ± 84	608 ± 28	0.001
RBC units	2 ± 0.7	3.4 ± 1.3	0.05
Total blood products	2.3 ± 1.0	6.8 ± 5.1	0.01

RBC = red blood cells; total blood products = RBC + plasma + platelet units.

These results support those of previously published studies in showing that the improved postoperative platelet function after administration of aprotinin is associated with reduced requirements for blood transfusion, thus reducing the risk of exposure to bloodborne viruses. Although the use of high-dose aprotinin increases the cost of operations, this increase is balanced by the reduced use of homologous blood products.

In conclusion, we recommend routine use of aprotinin in patients undergoing heart procedures with the potential for increased blood loss, such as redo operations or procedures requiring a prolonged period of CPB.

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Surgical Complications in Bridging to Transplantation: The Thermo Cardiosystems LVAD

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Left ventricular assistance with a number of different devices has been used to successfully bridge patients to cardiac transplantation. Surgical complications or complications related to the device itself, however, may preclude transplantation or lead to death. We report our recent experience with the Thermo Cardiosystems model 14 "HeartMate" left ventricular assist device in 3 patients. The device was implanted for 15 to 95 days. Complications included mediastinitis and peritonitis associated with the device in place before transplantation, and colonic perforation, and a late diaphragmatic hernia after transplantation. Despite these and other minor complications, all 3 patients underwent successful cardiac transplantation. Mechanical support for the right ventricle was not necessary. The Thermo Cardiosystems left ventricular assist device provided excellent support in a range of physiological conditions with no mechanical malfunction despite the surgical complications.

(Ann Thorac Surg 1992;53:482–6)

Cardiac transplantation as a therapy for end-stage heart disease became increasingly successful during the 1980s. However, the rapid growth of the procedure and the growing number of candidates for such therapy have not been accompanied by a similar increase in the availability of donor hearts. The resultant prolongation of the waiting period has predictably led to significant mortality among potential heart transplantation recipients awaiting a suitable donor organ [1, 2].

In spite of liberalization of donor criteria, a growing number of patients have become candidates for the use of mechanical assistance as a "bridge" to cardiac transplantation. The success of such a strategy using several available devices is well documented [3–6]. We report here our experience with bridging 3 critically ill patients to cardiac transplantation using the Thermo Cardiosystems (TCI) model 14 "HeartMate" left ventricular assist device (LVAD). The effort was successful in spite of important early and late complications.

Material and Methods

Description of Device

The TCI model 14 "HeartMate" LVAD is a totally implantable, pneumatically driven device. The pump is positioned intraperitoneally in the left upper quadrant with the driveline brought out through the abdominal wall and attached to a portable console. The inflow conduit penetrates the left ventricular apex and crosses the diaphragm to the pump (Fig 1). The outlet, a 25-mm Dacron graft, crosses anterior to the diaphragm near the midline and then is anastomosed to the ascending aorta. Porcine xenograft valves are used for both inflow and outflow conduits. All other internal blood-contacting surfaces are lined with either sintered titanium or textured polyurethane to promote formation and adherence of a pseudointima. Anticoagulation with crystalline warfarin sodium (Coumadin; Du Point Pharmaceuticals, Wilmington, DE), therefore, is not required, and most patients are maintained with 80 mg of aspirin daily. The pump has a stroke volume of up to 83 mL and is capable of a flow of 10 L/min. The drive system is a self-contained console that uses both alternating current and rechargeable batteries.

Patient Selection Criteria

In 1990, the TCI LVAD was implanted as a bridge to cardiac transplantation in 3 patients who had been accepted as cardiac transplantation candidates at our institution and were awaiting suitable cardiac donors. Before implantation of the LVAD, all patients demonstrated profound hemodynamic instability with a cardiac index of less than 1.8 L/min, hypotension defined as systemic blood pressure less than 90 mm Hg, and pulmonary congestion with a pulmonary capillary wedge pressure greater than 25 mm Hg, in spite of increasing doses of inotropic medications. None of the patients were intubated before implantation. Reduced renal blood flow, manifested by an elevation of the serum creatinine level, and falling urine output were further evidence of hemodynamic deterioration. All 3 patients were receiving at least three inotropic drugs before implantation of the LVAD, and 1 patient was supported with an intraaortic balloon pump in addition to medications.

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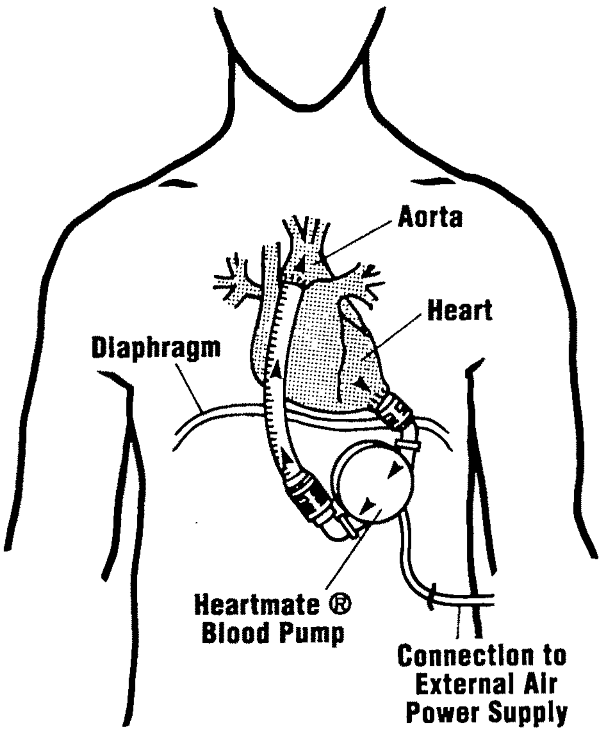

Fig 1. Air-driven ventricular assist device system.

Case Reports

Patient 1

A 51-year-old man sustained a massive anterior wall myocardial infarction in September 1989. Recurrent episodes of congestive heart failure developed, and he was found to have an ejection fraction of 0.16. He was accepted as a candidate for cardiac transplantation in January 1990. Shortly thereafter, he was admitted to Fairfax Hospital because of worsening congestive heart failure.

As the patient was unresponsive to multiple inotropic agents, the TCI LVAD was inserted on February 1. His postoperative course was unremarkable. Within 2 weeks of implantation of the device, he was ambulating in the hall as well as using an exercise bicycle. Thirty-eight days after LVAD insertion, a suitable donor heart became available, and the patient underwent removal of the LVAD and uneventful cardiac transplantation. He did well postoperatively and was discharged from the hospital 3 weeks after the transplant procedure.

Eight months later, abdominal discomfort, nausea, and vomiting developed. Workup revealed herniation of abdominal organs through a defect where the inflow conduit had penetrated the diaphragm. A laparotomy was performed with reduction of the omentum, colon, and part of the stomach, which had herniated into the pericardium and left pleural cavity. His recovery was rapid, and currently he is well 13 months after cardiac transplantation.

Patient 2

A 40-year-old man underwent aortic valve replacement and single-vessel coronary artery bypass grafting in June 1989 for endocarditis and embolic obstruction of the left anterior descending coronary artery. Subsequently progressive heart failure developed. He had an ejection fraction of 0.09 and was accepted for cardiac transplantation in March 1990 after evaluation. Several weeks later, he was readmitted to Fairfax Hospital because of worsening cardiac failure. Over a 4-week period, progressive hemodynamic deterioration occurred in spite of increasing doses of inotropic agents.

On May 2, after insertion of an intraaortic balloon pump resulted in no improvement, the patient underwent implantation of a TCI LVAD without difficulty. His immediate postoperative course was remarkable for recurrent lower gastrointestinal hemorrhage. Because of the Starr-Edwards aortic valve in his own heart, the patient had to be maintained on a regimen of heparin sodium, which contributed to the ongoing gastrointestinal bleeding. In addition, he had a chest tube site infection with *Staphylococcus aureus* accompanied by bacteremia, which responded to a regimen of appropriate antibiotics.

Fifteen days later, when a suitable donor heart became available, the patient underwent removal of the LVAD and cardiac transplantation. Intraoperative cultures of a purulent exudate in the chest tube tract revealed *S aureus*. Administration of antibiotics was continued for 4 weeks. Mediastinal exploration was prompted 12 hours postoperatively by a picture consistent with cardiac tamponade. At exploration, however, the patient was found to have substantial right heart failure, which subsequently responded to appropriate pharmacological intervention.

One week after transplantation, increasing abdominal pain developed, and a large amount of free air was noted on roentgenogram of the abdomen. At laparotomy, the patient was found to have a perforation of the transverse colon, which was thought to be related to division of dense adhesions between the colon and the LVAD driveline at the time of pump explantation. A transverse loop colostomy was performed. He sustained no further complications and was discharged 5 weeks later. The colostomy was closed after 10 months. The patient has recovered fully and is doing well approximately 12 months after cardiac transplantation.

Patient 3

A 22-year-old man had idiopathic cardiomyopathy and an ejection fraction of 0.09. He was accepted as a candidate for cardiac transplantation in April 1990. Subsequently intermittent episodes of ventricular tachycardia requiring antiarrhythmic therapy occurred as well as progressive heart failure despite intravenous inotropic management. On May 1, the TCI LVAD was inserted.

Three days after placement of the LVAD, pneumonia developed, and the patient was placed on a regimen of imipenem and vancomycin. Cultures, however, were negative. On the sixth postoperative day, there was a partial dehiscence of the midline abdominal incision, and the patient underwent reexploration. Blood-tinged ascites was present, and intraoperative cultures were negative. A segment of Marlex mesh was necessary for reclosure to reduce tension. Administration of antibiotics was continued, and fluconazol was added when signs of sepsis developed, including temperature of 40°C, hypotension, and leukocytosis (white blood cell count greater than 30 × 10^9/L [30,000/μL]).

When purulent drainage from the incision occurred, the patient again underwent reexploration. Extensive purulent mediastinitis and peritonitis involving the LVAD, inflow and outflow cannulas, and driveline were noted. Vigorous irrigation and debridement of the wound were carried out, and continuous irrigating catheters were placed. The wound was continuously irrigated with 1.0% povidone-iodine solution for 2 weeks. The pump continued to function normally during this time with cardiac outputs in excess of 10 L/min. Wound cultures were negative despite definite signs of sepsis, probably because of extensive antibiotic coverage. The patient had a slow but gradual recovery, complicated only by a sacral decubitus ulcer, which ultimately required debridement and flap closure.

Ninety-five days after placement of the LVAD, a suitable donor heart became available, and explanation of the LVAD and cardiac transplantation were performed without difficulty. There were no signs of mediastinitis or peritonitis at the time of this operation, although some exudate was noted near the inflow cannula and anterior to the LVAD. Cultures were negative. The patient did well after transplantation and was discharged home 3 weeks later. At 9 months after transplantation, he is currently having no difficulties.

Comment

The use of a mechanical device as a "bridge" to transplantation was introduced by Cooley and associates [7] in 1969. A pneumatically powered total artificial heart was used to sustain life for 64 hours until a suitable donor heart became available. The patient died 32 hours after cardiac transplantation. The feasibility of staged cardiac transplantation by maintaining critically ill patients on mechanical support until cardiac transplantation could be performed had been demonstrated.

Successful bridging to cardiac transplant procedures with intraaortic balloon pumps was reported during the latter half of the 1970s and early 1980s [8, 9]. In September 1984, the first successful use of a ventricular assist device as a bridge to transplantation was performed by Oyer and colleagues using a Novacor left ventricular assist system [10]. Hill and associates accomplished the second successful bridging procedure only 1 day later using a Thoratec Pierce-Donachy pneumatic LVAD [11]. Since that time, a number of groups [12–15] have reported success with these and other LVADs in bridging patients to transplantation. Successful bridging to transplantation has occurred in up to 75% of patients receiving mechanical devices. Reported rates of success have varied depending on the device and the patient selection criteria. Once transplantation has been performed, survival is nearly equal to that in patients undergoing transplantation without bridging [3–6].

While supported by the device, however, a number of patients experience major complications that preclude transplantation. Sepsis, multiorgan failure, and bleeding remain the most common causes leading to death before transplantation [12–14]. Nevertheless, some patients can overcome major complications during mechanical support and survive to successful transplantation. Although 2 of our 3 patients experienced substantial morbidity while the LVAD was in place, all had successful outcomes.

Thromboembolic events have not been a problem with the TCI LVAD in spite of minimal anticoagulation [16]. However, we noted thrombus formation on the struts of the Starr-Edwards valve explanted with the heart of 1 patient at transplantation, and a cerebrovascular accident occurred in another patient with a TCI LVAD and mechanical valve in place (Dasse K, personal communication, 1991). A mechanical aortic valve may be a contraindication for use of an LVAD. Hemolysis was not a problem, and all devices continued to function admirably with cardiac outputs of up to 10 L/min in spite of sepsis in 2 of our patients. The TCI LVAD has been easy to implant, and the single percutaneous driveline permits early and easy patient ambulation.

A major limitation of a device that supports only the left ventricle can be seen in patients who demonstrate major right heart failure before or after implantation. Although treatment with prostaglandins and other vasodilators has proved to be beneficial in relieving right heart failure in some patients [17], temporary support of the right ventricle can sometimes be necessary. Like others, we have found that with this device, which is capable of high output, right ventricular support may not be required in nearly as many patients. At present, there are no clear indicators available to determine which patients will require additional right ventricular support before placement of an implantable LVAD [12, 18].

In spite of major complications in each of our 3 patients, the TCI LVAD provided excellent and reliable hemodynamic support. All of our patients were extubated and ambulatory by the time a suitable donor heart became available. Two of the patients had potentially life-threatening infections that cleared despite the presence of a large foreign body in the mediastinum and abdomen. Because of echocardiographically documented movement of the poppet in the Starr-Edwards valve, one of our patients required heparin, which complicated the postoperative course. The other 2 patients, maintained on only 80 mg of aspirin daily, had no evidence of thromboembolism. This greatly simplified the subsequent operative closure of the decubitus ulcer in 1 of them.

Although there was early evidence of right ventricular dysfunction in 2 of our 3 patients, both responded to prostaglandin therapy. We are in agreement with Kormos and co-workers [18] that a majority of patients awaiting cardiac transplantation can successfully be bridged with left ventricular support alone provided they have a normal pulmonary vascular resistance and there is complete unloading of the left atrium to further reduce afterload on the right ventricle. Occasional patients with fixed pulmonary hypertension or acute pulmonary disease and right heart dysfunction may require right ventricular support.

The majority, however, should not require long-term assistance.

In conclusion, with the growing shortage of donor organs and the expanding success of cardiac transplantation, there will be an increasing need for a mechanical alternative to transplantation. The need for a totally implantable, self-contained ventricular assist device is apparent. Clinical testing of a forerunner of such a device, the TCI vented electric pump, has recently been approved and has commenced under an investigational device exemption from the Food and Drug Administration. This device has a percutaneous wire and vent, which allow for portable operation with the use of a pager-sized electronic controller worn on the belt and battery packs worn in shoulder holsters, which will allow up to 8 hours of untethered function. The device can also be attached to an external power source. Recent long-term support of patients awaiting cardiac transplantation has indicated the probable success of such devices.

This report of 3 patients further supports the utility of the TCI LVAD to provide temporary or long-term circulatory support for patients in a severely compromised hemodynamic state who are awaiting cardiac transplantation. The device is relatively easy to implant and operate and is capable of an effective response to wide variations in physiologic needs. Despite major surgical complications, including mediastinitis, colonic perforation, and a diaphragmatic hernia, all of our patients have done well. Biventricular assistance was not necessary. Our encouraging results and those in other centers justify the current use of left ventricular assistance as an adjunct now, and eventually as an alternative to cardiac transplantation in the future.

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INVITED COMMENTARY

This article focuses our attention on three surgical complications associated with the use of the TCI LVAD, which could just as well be any abdominally located LVAD: wound infection and dehiscence, diaphragmatic hernia, and colon perforation.

These complications hint at an important aspect of prosthetic device design and clinical applications that we sometimes lose sight of in this multifaceted, future-driven technology. A prosthetic device must be designed to adapt to the patient and not the patient to the device. In each of these three illustrated case histories the mechanical heart pump performed flawlessly to pump blood and support the metabolic needs of the patient, but the physical design, weight, and anatomical location of the device caused serious and life-threatening patient morbidity to adjacent tissues and organs. In an ill-founded optimism we somehow think the body might attenuate some of its biological restraints as a trade for getting improved cardiac output, and consequently we sometimes overestimate the body's capacity to accommodate the purely physical aspects of a device. It does not work that way. In this report the successful outcome each of these patients eventually enjoyed is a tribute to the surgical skill of the attending physicians and modern antibiotics. We will not always be that fortunate.

It would be prudent to address some of the questions and options that occurrences such as these complications stimulate. Three things come to mind. Is this part of the learning curve of a new device while the surgical community works out the ambiguities of its clinical application? Is this a patient selection issue in which certain patient characteristics would exclude them as candidates (eg, small body size, previous abdominal operation, poor nutrition)? Or is there a fundamental flaw in the strategy of locating what will be a permanent cardiac support device in the abdomen due to certain weight, size, and shape specifications that cannot be traded down to make the abdomen a safe location?

Certainly there are truths in each of these possibilities. Time, innovation, perseverance, and the accumulation of surgical experience will accompany the eventual solution. But a common denominator of any biological-mechanical interface will be the design that melts into the body's architecture and chemistry without expecting it to make substantial adaptations. That is a principle we cannot forget, and complications such as noted in this excellent article are examples.

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Experimental In Vitro Endothelialization of Cardiac Valve Leaflets

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This study reports our results with in vitro endothelialization of fresh nonpreserved homograft valve leaflets compared with mild alternatively preserved valves and valves treated by preservation procedures commonly used for commercially available tissue valves. In vitro lining of biological heart valves with cultured autologous endothelial cells might help prevent the detrimental effects of degeneration on valve durability. To investigate the growth characteristics of endothelial cells on valve bioprostheses, three different methods of storage and preservation were compared. After precoating with fibronectin and seeding of 4.4 × 10^4 endothelial cells/cm^2 onto the different leaflet surfaces, primary adherence, growth kinetics, morphology, and maintenance of monolayer integrity were studied over a period of 10 days. On valve leaflet surfaces of group 1 (fresh nonpreserved homograft valve leaflets) and group 2 (mild alternatively preserved valves), endothelial cells grew to persistent monolayers between days 6 and 10. In contrast, endothelial cell proliferation with monolayer growth could not be achieved on the group 3 leaflets (preserved like commercially available biological valve prostheses). In that group, no viable endothelial cells could be found on the valve surfaces 2 days after seeding. These results demonstrate the theoretical feasibility of endothelializing biological heart valve leaflets in vitro if they are not preserved and stored according to commonly used procedures. Provided such an endothelium can withstand the mechanical forces after implantation in vivo, in vitro endothelialization might contribute either to the development of new biological heart valves for modern cardiac surgery or to the improvement of clinical results with homograft valve transplants.

(Ann Thorac Surg 1992;53:487–92)

Complications related to cardiac valve prostheses can frequently necessitate reoperation or cause death, and now occur in approximately 5% to 15% of all valve procedures [1]. The major cause of dysfunction of cardiac valve bioprostheses is tissue degeneration, especially cuspal mineralization [2]. It necessitates reoperation in 20% to 25% of recipients within 7 to 10 years postoperatively [3]. Specific implant and host factors regulating the calcification of bioprosthetic tissue have been clarified [4], but exact underlying mechanisms of such mineralization are essentially unknown [5]. Many reasons have been given to explain dystrophic calcification of fixans-processed bioprostheses: (1) cross-linking or collagen breakdown by glutaraldehyde [5]; (2) carboxyglutamic acid–containing plasma protein insudation abetted by the loss of a viable endothelial cell barrier [6]; (3) removal of proteoglycans during commercial processing [7]; (4) organization of thrombi generated as a result of the lack of endothelial cell coverage [8]; and (5) cytotoxic reactions caused by the slow leaching of chemicals used for cross-linking and sterilizing [9].

For editorial comment, see page 371.

It may be postulated that the "ideal" biological valve has not yet been found and that this "ideal" bioprostheses will be a valve that possesses a confluent monolayer of viable autogenic endothelial cells and does not release toxins. In previous studies [9] it has been shown that extracts obtained from glutaraldehyde-fixed cardiac valve prostheses are typically highly cytotoxic. Also, it was demonstrated that residual effects of glutaraldehyde can be detected in animal tissue as long as 6 months after implantation of glutaraldehyde-tanned collagen sponges [10]. Subsequent experiments [11] confirmed that released toxins in glutaraldehyde-preserved pericardial tissue or porcine valves inhibit endothelial cells from covering the graft surface.

As an alternative to mechanical or glutaraldehyde-preserved valves, the transplantation of allograft aortic valves was first reported by Ross, Barratt-Boyes, and others in 1962. Increasing evidence accumulated to suggest that this viable valve tissue was likely to be superior to nonviable tissue because it could be shown that sterilization and preservation influence valve durability [12]. Nevertheless, the histological changes found in fresh allografts that have been implanted in patients are essentially the same as those in chemically sterilized [13] and antibiotic-treated allografts [14]: the predominant structural changes involve the loss of donor leaflet endothelium with subsequent disorganization of underlying collagen fibers, subsequent fibroblast necrosis, gross leaflet thickening, and finally degeneration of the allograft, al-

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though absence of calcification is observed [14, 15]. Therefore, for the durability of viable allografts as well as alternatively preserved biological valves, it may be important to have viable autogenic endothelial cells to maintain complete physiological function of the valve, which may prevent subsequent degeneration.

To find a treatment for tissue valves that will ultimately allow complete endothelial cell lining, we studied the growth behavior of endothelial cells on homograft valve surfaces. In addition, we used this experimental model to study the influence of a mild alternative fixans-processing technique on endothelial growth behavior on these valve leaflets.

Material and Methods

Allograft valves were procured from cadavers at autopsies less than 48 hours after death. The tissue removed included the aortic and pulmonary valves, which were roughly dissected under clean, but not sterile, conditions. The valves were rinsed in saline solution (0.9%), trimmed of excess tissue, and placed immediately into a nutrient-antibiotic solution: modified M-199 medium (Gibco Laboratories, Life Technologies Inc, Grand Island, NY) with Earle's salts, sodium bicarbonate (2.2 g/L) without glutamine, and 10% fetal bovine serum (FBS) (Flow Labs, Irvine, Scotland) containing piperacillin solution (1.0 mg/mL) (Cyanamid GmbH, Wolfratshausen, Germany), polymyxin E (0.17 mg/mL) (Gruenenthal GmbH, Stolben, Germany), and nystatin (0.5 mg/mL) (v. Heyden GmbH, Munich, Germany). The harvested allografts were randomly divided into three experimental groups: group 1, nonpreserved valves; group 2, alternatively preserved valves; and group 3, valves preserved like commercially available tissue valves.

Storage and Preservation

Allograft valves chosen for group 1 were left in the nutrient-antibiotic solution at 4°C for a minimum of 10 days, but not longer than 2 weeks.

Allograft valves chosen for group 2 were left for 30 minutes in 0.25% glutaraldehyde (Fluka AG, Buchs, Switzerland) in phosphate-buffered saline solution (Flow Labs), followed by rinsing with saline storage medium in M-199 medium with 10% FBS at 4°C. Rinsing was repeated three times for 30 minutes before the leaflets were stored in the nutrient-antibiotic solution at 4°C for a period not longer than 2 weeks.

Allograft valves chosen for group 3 were preserved according to the procedure commonly used for commercially available tissue valves: preserved in 0.5% glutaraldehyde for 48 hours, transferred into 6% formaldehyde for 12 hours, and then stored in 50% ethanol.

Preparation of Valve Leaflets

After the valves were removed from their respective storage solutions, the leaflets were rinsed in sterile saline solution (0.9%) twice for 30 minutes and then were left in saline solution for 24 hours. Then the valve leaflets were trimmed into round patches 1 cm in diameter. The leaflet surfaces were gently rubbed to remove remaining donor endothelium.

Valve leaflets were kept in FBS for 24 hours before precoating with fibronectin (28 μg/mL) (HFN; Inotech, Zurich, Switzerland) at room temperature for 4 hours.

Cultivation of Bovine Aortic Endothelial Cells

Bovine aortic endothelial cells were grown from bovine aortic segments, collected in Vienna from a slaughterhouse. The bovine aortic endothelial cells were isolated and cultivated according to the procedure described by Macarak and associates [16]. The cells were harvested by exposure of the aortic segment to collagenase type II (CLS II; Cooper) for 15 minutes at 37°C, seeded into 150-cm^2 culture flasks (Falcon) precoated with 28 μg/mL of fibronectin, and grown to confluence. The culture medium was a minimum essential medium (D-Val; Flow Labs), containing L-glutamine (2 mmol/L), 10% FBS, preservative-free heparin sodium (17.5 U/mL) (Sero-Med, Vienna, Austria), endothelial cell growth factor (300 μg/mL) (Collaborative Research, Lexington, MA), penicillin (80 U/mL) (Gibco), and streptomycin sulfate (80 μg/mL) (Gibco). Cell cultures were incubated at 37°C in a humidified atmosphere of 5% carbon dioxide in air. Trypsin-EDTA solution (0.025%:0.02%) (Inotech) was used for cell passage, and FBS was added to inactivate any residual trypsin. All bovine aortic endothelial cell cultures were identified by factor VIII rAG staining and by the typical "cobblestone" contact-inhibition morphology on scanning electron microscopy (SEM).

An initial cell count was performed before centrifugation of the endothelial cell/serum suspension to allow adjustment of the cell number to the final seeding density.

Endothelialization

After centrifugation, the endothelial cells were resuspended in medium D-Val with 20% FBS and endothelial cell growth factor (3 mg/mL) and seeded onto the valve leaflet surfaces at a final density of 4.4 × 10^4 endothelial cells/cm^2. Each valve leaflet was placed into a 24-well plate (Falcon) containing a total nutrient volume of 2 mL of medium and was kept under a glass ring with an inside square area of 0.8 cm^2 (Fig 1). This allowed a reproducible culture area and also kept the valve patches from swimming up in the culture medium. The cells were fed three times a week.

Parallel to all series of experiments, separate cultures of bovine aortic endothelial cells from the same cultures used for endothelialization of the valve leaflets were grown in 24-well plates as control cultures with an initial seeding density of 4.4 × 10^4 endothelial cells/cm^2 and cultivated for 10 days (group 4).

Cell Kinetic Studies

For each single experiment, 8 valve leaflets from each group were seeded. On days 1, 3, 5, 7, and 10, the cell count was obtained by sacrificing 2 of the valve leaflets. To facilitate counting, the valve leaflets were mounted on a stainless steel frame that prevented detachment of the material. The samples were rinsed in phosphate-buffered

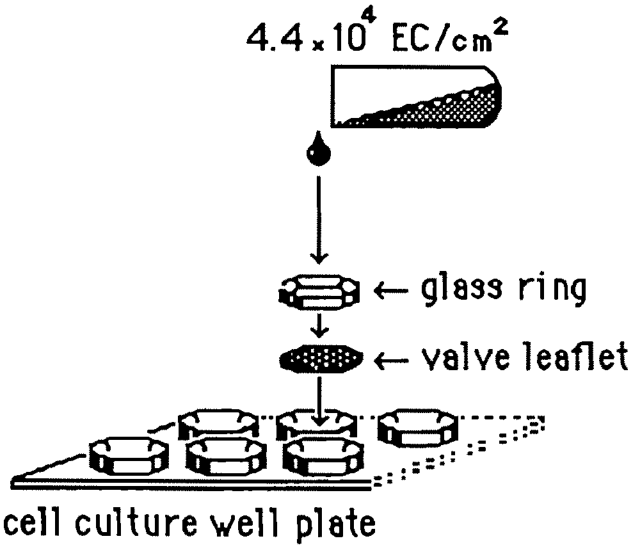

Fig 1. Experimental setup: after seeding of endothelial cells (EC) on valve leaflet surfaces, the patches of leaflet were placed into a 24-well plate and kept under a glass ring. This allowed a reproducible culture area and prevented the valve patches from swimming up in the culture medium.

saline solution and 200 μL of distilled water, frozen to −70°C followed by warming to +60°C, and treated with ultrasound for 2 minutes. Then 200 mL of crystal violet was added. The cell counts were determined by means of the crystal violet method in a Buerker Tuerk counting chamber [17]. In a parallel series, endothelial cells were harvested with trypsin–EDTA solution (0.025%:0.02%) from the valve leaflet surface, and cell counts were determined in a hemocytometer. In addition, the reliability of this procedure was controlled by scanning electron microscopic studies of untreated and crystal violet–treated samples.

Nine subsequent series of experiments were performed in group 1 (72 valve leaflets), ten in group 2 (80 valve leaflets), and seven in group 3 (56 valve leaflets).

Scanning Electron Microscopy

Parallel to all series of experiments, separate experiments were performed for SEM. Fixation procedures for SEM followed the method of Schroetter and associates [18]. A JEOL JSM T 20 scanning electron microscope was used.

Thymidine Incorporation

Details of the proliferation assay, based on the incorporation of tritiated thymidine into macromolecules by subconfluent, actively replicating cells in the log phase of growth, have been described elsewhere [19]. Separate experiments for thymidine incorporation were performed, and counts were obtained on days 1, 3, 5, 7, and 10. Endothelialized valve leaflets were incubated with 5 μCi/mL of methyl-^{3}H-thymidine per well (185 GBec, 5.0 Ci/mmol, ≅5 mL Amersham International plc. TRA 120 Batch 278) for 24 hours followed by a rinsing procedure with 20% FBS in phosphate-buffered saline solution without Ca^{2+} and Mg^{+}, repeated three times for 30 minutes. Then trypsin was added for 30 minutes, and counting was done with a 1211 Rackbeta Liquid Scintillation Counter (LKB Scintillation Products, Wallac).

Separate cultures of bovine aortic endothelial cells (group 4) were counted as control. In addition, untreated valve leaflets that were not seeded with endothelial cells were counted to obtain blank values, and all results were expressed as percentages of those produced by these untreated valve leaflets to allow comparison between different experiments.

Statistical Analysis

Statistical analysis was done by means of Tukey's studentized range (HSD) test. Significances were calculated for the comparison of the different preparations of valve leaflets and for the time course of observations.

Results

Figure 2 shows the experimental results of cell counts and tritiated thymidine counts, representative of the proliferative capacity of endothelial cells cultivated on differently treated valve leaflet surfaces. On the valve leaflet surfaces of group 1 and group 2, endothelial cells grew to persistent monolayers between days 6 and 10. In contrast, endothelial cell proliferation with monolayer growth could not be achieved on the group 3 leaflets. In that group, no viable endothelial cells at all could be found on the valve surfaces 2 days after seeding.

Group 1

On nonpreserved allograft valve leaflet surfaces, 25.1% ± 12.5% of seeded endothelial cells were found to adhere on day 1. Thus, the initial day-1 cell density was 1.1 ± 0.6 × 10^4 endothelial cells/cm^2. Tritiated thymidine incorporation was found to be 22.3% ± 5.7% compared with the control untreated valve leaflets. On day 5, the cell density increased to 4.9 ± 0.8 × 10^4 endothelial cells/cm^2, and the peak of tritiated-thymidine incorporation (187.3% ± 28.2%) was identified, indicative of the fastest endothelial cell proliferation, which began after a lag phase of 4 days after endothelial cell seeding. The light microscopic appearance of endothelial cells was characterized by a preconfluent monolayer with occasional cell-free areas. Scanning electron microscopy showed spindle-shaped endothelial cells with moderate marginal overlapping. Until day 10, a distinct endothelial cell proliferation (to mean values of 9.8 ± 1.2 × 10^4 endothelial cells/cm^2) occurred. At that point, endothelial cell morphology had mostly changed from spindle-shaped to polygonal, resulting in a cobblestone pattern found only in ideally cultivated endothelial cell monolayers. Tritiated thymidine incorporation had decreased to nearly zero after day 7, indicative of the low proliferation rate of endothelial cells in a cobblestone monolayer.

Group 2

Endothelial cell adherence was achieved on all valve leaflet surfaces on day 1. The overall primary adherence

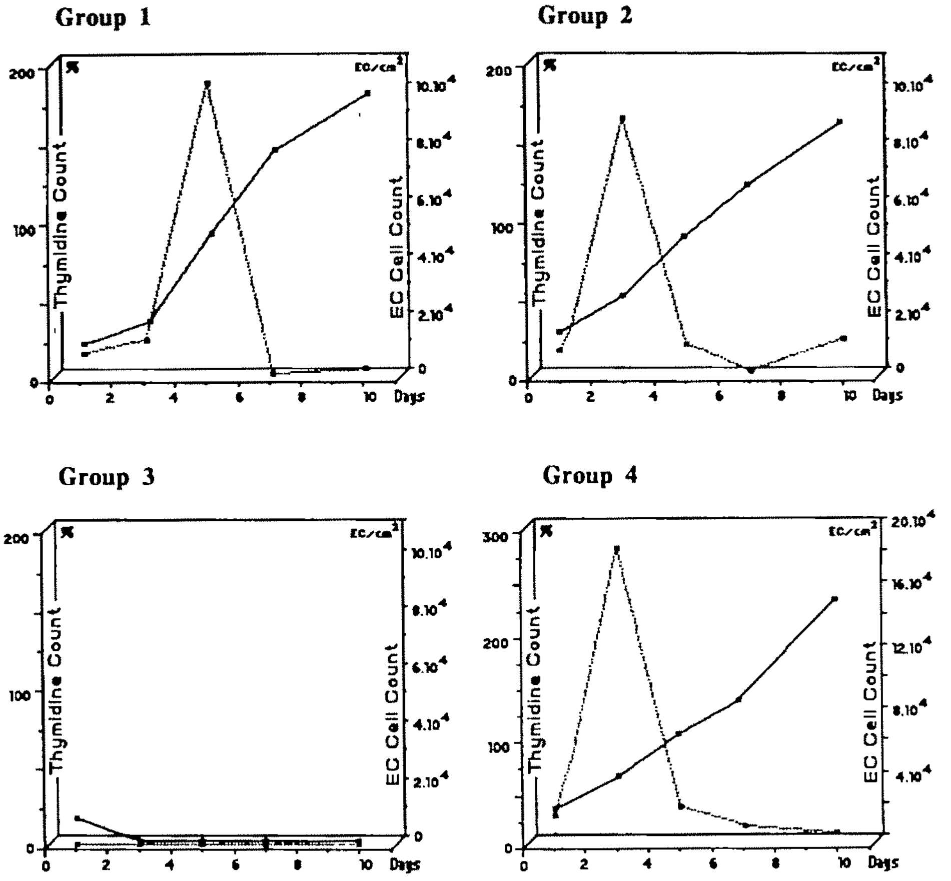

Fig 2. Proliferative capacity of endothelial cells (EC) cultivated on differently treated valve-leaflet surfaces: group 1, fresh nonpreserved homograft valve leaflets; group 2, mild alternatively preserved valves; group 3, valve leaflets treated according to preservation and storage procedures commonly used for commercially available tissue valves; and group 4, control group of the same bovine aortic endothelial cell cultures used for endothelialization of valve leaflets and grown in 24-well plates. Endothelial cell count is plotted as a solid line *and tritiated thymidine count, as a* broken line. *Right ordinate shows endothelial cell density (EC/cm²) and left ordinate, growth-promoting activity expressed as percentage of tritiated thymidine counts produced by untreated valve leaflets.*

(31.8% ± 14.8%) was higher than in group 1, and the initial mean cell density on these surfaces was 1.4 ± 0.7 × 10^4 endothelial cells/cm². Under light microscopy, endothelial cells appeared in cell clusters, and SEM showed spindle-shaped endothelial cells with beginning marginal overlapping. In contrast to group 1, the peak of tritiated thymidine incorporation (174.7% ± 31.5%) was identified on day 3 after seeding ($p < 0.001$). Through day 10, the proliferative capacity of endothelial cells was comparable in both groups 1 and 2. In ten series of experiments, the day-10 cell density was 8.0 ± 0.2 × 10^4 endothelial cells/cm². With SEM, adjacent endothelial cells showed distinct marginal overlapping, and the morphological appearance was of a preconfluent monolayer with spindle-shaped cells instead of the typical cobblestone pattern. Tritiated thymidine incorporation of endothelial cells on valve leaflet surfaces increased to 28.3% ± 17.5% ($p < 0.05$ compared with group 1) on day 10 from nearly zero on day 7, indicative of minor proliferative activity, which might be caused by endothelial cell loss in small numbers because of slow leaching of chemicals used for valve preservation, although endothelial cell coverage of the leaflet surfaces was observed.

Group 3

Initial endothelial cell adherence was 13.6% ± 2.2% on the leaflets of valves treated like the commercially available valves. This day-1 value represents the lowest initial cell adherence of the three groups, with resulting mean cell densities of 0.6 ± 0.1 × 10^4 endothelial cells/cm² ($p < 0.05$). Under the scanning electron microscope, only a few single islands of a few endothelial cells were found to have remained. They appeared to be loosely adherent and were mostly lacking microvilli. No subsequent endothelial cell proliferation was observed on these valve leaflet surfaces thereafter, and SEM showed denuded leaflet surfaces with no viable endothelial cells after the second day of cultivation. Furthermore, tritiated thymidine incorporation showed no growth activity at all and remained at the zero level.

Group 4

Normal endothelial cell growth behavior could be observed in the control cultures (grown in 24-well plates). Initial cell adherence was 40.9% ± 20.4% on day 1, with a resulting mean cell density of 1.8 ± 0.9 × 10^4 endothelial cells/cm². Through day 10 of cultivation, endothelial cell proliferation to a mean value of 15.3 ± 1.2 × 10^4 endothelial cells/cm² occurred, and light microscopy as well as SEM revealed the normal cobblestone morphology of the confluent endothelial cell monolayer. The peak of tritiated thymidine incorporation (179.4% ± 18.5%) was identified on day 3.

Overall Growth Behavior

For valve leaflets in groups 1 and 2, endothelial cell growth was significantly better ($p < 0.001$) than that for group 3 leaflets, on which no growth at all could be found. There was no significant difference between the group 1 and group 2 valve leaflets and the endothelial cell growth behavior of the group 4 control cultures ($p > 0.1$).

Comment

The experimental model of human homograft valve leaflets was chosen because it allowed easy access to this type of valve for our laboratory experiments and because using valve leaflets of the same type and origin allowed us to study the influence of valve-preservation techniques on endothelial cell growth. Furthermore, using human homograft valves also allowed us to investigate the possibility of in vitro endothelialization of nonpreserved valves, which have been in clinical use since the first transplantation of aortic homografts in 1962 [12] but have been described to undergo degeneration subsequent to implantation, probably because of the lack of a viable endothelial cell layer on the surfaces [13–15].

Complications associated with biological valve prostheses are caused for the most part by dysfunction resulting from tissue degeneration and cuspal mineralization [2] and may be explained by the dystrophic effects of fixans-processing [7, 9]. The absence of viable endothelium also may contribute to tissue degeneration: it favors plasma protein insudation [6] as well as the organization of thrombi [8]. In viable homograft valves, the lack of viable endothelium was shown to cause deterioration of fibroblast function, which subsequently influenced the integrity of the leaflet matrix [20]. In addition, immunological attacks may be prevented by in vitro lining with autogenic endothelium, as surface-antigen–positive donor endothelial cells have been found on cryopreserved homograft valves [21], and fibrous dysplasia and patchy necrosis of valve tissue have been described as chronic immunological rejection in fresh valve transplants [22].

Our comparative study of in vitro endothelial cell proliferation and morphology of differently treated valve surfaces clearly favors either nonpreserved valves (like commonly used homograft valves) or valves preserved with a mild alternative fixans-processing technique. Valves of these two groups showed endothelial cell growth behavior as well as morphological signs of monolayer integrity comparable with those of the control cultures of the same endothelial cell populations. Valve leaflets preserved according to common commercial fixans-processing techniques are not suitable for in vitro endothelialization. Morphologically, the remaining endothelial cells on these valve surfaces 2 days after seeding showed vacuolization or other signs of cell damage that would be expected in the presence of a toxic agent, and no proliferation at all could be found (see Fig 2). In contrast, the overall primary adherence of endothelial cells on surfaces of alternatively preserved valve leaflets (group 2) was higher than on nonpreserved valve leaflets (group 1), and SEM revealed spindle-shaped endothelial cells with beginning marginal overlapping. After 10 days of cultivation, SEM showed the morphological appearance of a preconfluent monolayer with spindle-shaped cells instead of the typical cobblestone pattern, which could be observed on nonpreserved valve leaflets (group 1) at the same time interval. This ideal morphological feature may be indicative of a "normal" cultivation condition found on fibronectin-coated nonpreserved leaflet surfaces of this group, although cell growth was not as pronounced as initially found on alternatively preserved valves, and the proliferation peak (according to tritiated thymidine incorporation) was delayed (see Fig 2).

The initial rapid cell proliferation on alternatively preserved valve leaflets (group 2), confirmed by the early peak of tritiated thymidine incorporation on day 3 (see Fig 2), and the morphological feature found might be due to a well-known effect of brief aldehyde treatment. This procedure has previously been described as promoting endothelial cell growth and was named "biolization" [23]. Moreover, it was demonstrated that fibronectin, which enhances endothelial cell adherence and proliferation [24], binds specifically to type I collagen [25] and that this binding capacity can be drastically increased by denaturing collagen [25]. Because type I collagen is found on the surfaces of fibrocytes and fibroblasts, the brief treatment of the valve leaflet with glutaraldehyde can be expected to result in a particularly high fibronectin concentration at the leaflet surface.

In summary, alternative preservation procedures that prove to have less toxic effects on valve tissue but nevertheless maintain mechanical durability of the leaflets in vivo as well as a confluent monolayer of viable autogenic endothelial cells covering the valve leaflet surfaces may help to prevent the detrimental effects of degeneration on valve durability. To prove the concept of alternative preservation and endothelialization of biological valves, long-term in vivo experiments should be performed. As one important prerequisite for rapid endothelialization of valve surfaces, the reliable cultivation of sufficient numbers of first-passage endothelial cells has been shown to be possible within a reasonably short period [26]. Furthermore, our previous experiments [17, 27] with a mechanical seeding device demonstrated that confluent endothelial cell monolayers could be achieved 3 hours after endothelial seeding. Adapting this concept by using a three-dimensional rotation device for valves may be easily possible. Even if a cultivation period of a few days after seeding is necessary to enable the maturation of the cytoskeleton [28], the endothelialization process would be possible within a few weeks.

A further unsolved problem is the question of shear stress resistance of endothelial cell monolayers cultivated on valve leaflet surfaces. Although we [17] have demonstrated the shear stress resistance of in vitro endothelialized vascular grafts in previous studies, the persistence of endothelial integrity during the movements of valves in the bloodstream after implantation may not be comparable with our results with vascular grafts, as valves in the heart are exposed to different flow patterns. Nevertheless, the formation of "dense peripheral bands," which are thought to be the site of strong cell adhesion [29], seems to require a cultivation period of 8 to 12 days [28]. Taking this delay into consideration, a two-step in vitro cultivation of endothelial cells on biological heart valves may be feasible to create a shear stress–resistant endothelial cell layer on the leaflet surface.

If future experiments can demonstrate persistence of monolayer integrity and continuing antithrombotic properties of cultured autologous endothelial cells on the surfaces of biological heart valves as well as reduced degeneration because of mild alternative fixation procedures and a confluent endothelial coverage, this concept might contribute either to the development of new biological heart valves for modern cardiac surgery or to the improvement of clinical results with homograft valve transplants.

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Surgical Decision Analysis: Esophagectomy/Esophagogastrectomy With or Without Drainage?

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Decision analysis was used to compare three management strategies for patients undergoing esophagogastrectomy for carcinoma of the esophagus or gastric cardia: drain all patients with either pyloromyotomy or pyloroplasty, drain no patient, or perform a test that stratifies patients into high-risk and low-risk groups for development of gastric outlet obstruction and drain the high-risk group. Results indicate that a "drain all" approach is appropriate in clinical settings where the risk of gastric outlet obstruction is greater than 10%, as long as the drainage procedure is 95% effective. If a test were developed to stratify patients, it would have to have a sensitivity of 80% when its specificity was 100%, and would require a higher sensitivity as the specificity fell below 100%.

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In 1948, Dragstedt and Camp [1] observed that symptoms of gastric stasis developed in 25% of patients who had undergone truncal vagotomy for duodenal ulcer disease. They thus advised the addition of a drainage procedure to truncal vagotomy for the treatment of duodenal ulcer disease. Whether patients with an intrathoracic vagotomized stomach after esophagectomy or esophagogastrectomy for carcinoma are at similar risk for development of symptoms of gastric stasis remains controversial. Some surgeons believe that drainage is as necessary in this setting as after truncal vagotomy for duodenal ulcer [2–7]. Other surgeons drain selectively [8, 9] or not at all [10–12], believing that the intrathoracic stomach empties well and that the risk of harmful bile reflux exceeds the possible benefit or need for a drainage procedure. The controversy continues because the few studies that have addressed the issue include too few patients, short follow-up times, different types of operation, and different drainage procedures [2].

For editorial comment, see page 373.

This article will apply decision analysis to the dilemma using a computer software program to create a model that explores all of the treatment options taking into account their attendant risks and benefits. Sensitivity analysis of the variables is undertaken to define thresholds to aid the clinician in choosing a therapeutic approach. To determine the best alternative for an individual patient, the risks and benefits of the drainage procedure and the accuracy of predicting an individual's risk must be considered.

Material and Methods

Question

Should all, some, or no patients undergoing esophagectomy or esophagogastrectomy with esophagogastrostomy for carcinoma of the esophagus or gastric cardia have a drainage procedure performed at the time of initial operation?

Model

DECISION TREE. The decision tree is illustrated in Figure 1. The model compares three strategic choices: treat all patients, treat no patient, or test patients and treat only those at high risk. The goal is to minimize the proportion of patients in whom any complication develops either as a result of gastric outlet obstruction or as a result of the drainage procedure.

If a clinician chooses the first branch of the tree, all patients will have a drainage procedure performed. This will expose all patients to the risk of a drainage-associated complication. If the procedure is not 100% efficacious, some patients will also develop gastric outlet obstruction. The signs and symptoms of gastric outlet obstruction and its sequelae are as follows: gastroesophageal reflux, regurgitation, aspiration pneumonitis, pneumonia, hoarseness, bezoar formation, stasis gastritis, gastric ulceration or bleeding, early satiety, bloating or eructation, and inability to maintain/regain weight.

If a clinician chooses the drain none branch of the tree, the outcome is determined by the risk of gastric outlet obstruction alone. If a clinician chooses the test branch, patients will be placed into high-risk and low-risk groups for development of gastric stasis based on their test result. Those considered to be at high risk will have a drainage procedure. Possible outcomes for these patients are similar to those in the drain all group, although the risk may be greater. Those considered to be at low risk will have a

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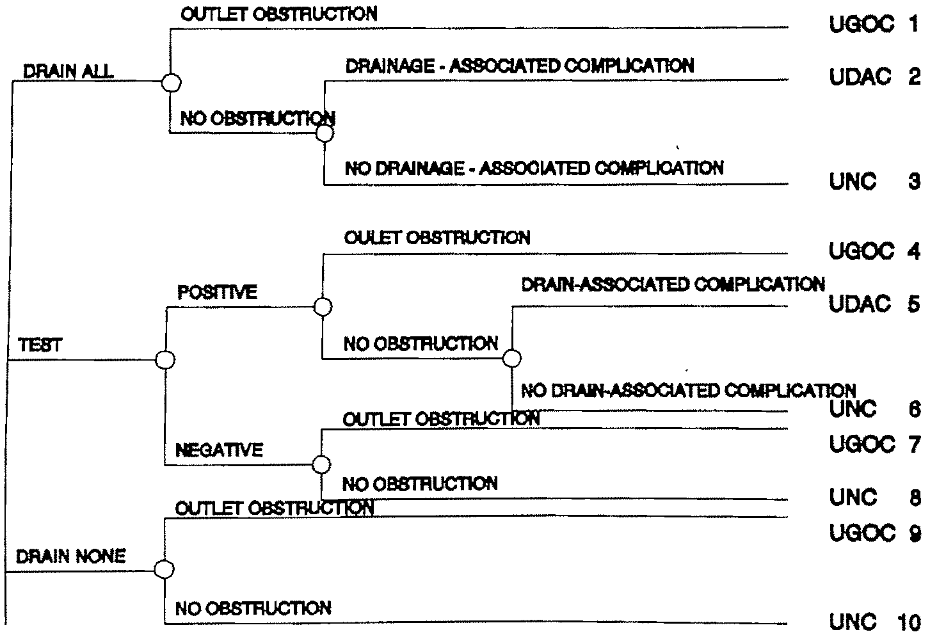

Fig 1. Decision tree of three approaches to gastric outlet drainage in patients undergoing operation for carcinoma of the esophagus or gastric cardia. (UDAC = *utility of drainage-associated complication;* UGOC = *utility of gastric outlet complication;* UNC = *utility of no complication.)*

less than or equal chance of development of gastric outlet obstruction compared with patients in the drain none branch providing the test is valid.

TEST. At the present time there exists no valid, reliable method of distinguishing between patients at high risk for development of gastric outlet obstruction and those at low risk. In this article, therefore, we propose a test based on clinical characteristics. Because the sensitivity and specificity of the test are unknown at this time, we will use sensitivity analysis to determine how accurate it would have to be to be useful. The questions in the test are largely based upon intuitive assessment (Appendix 1). There is no risk associated with the test.

DRAINAGE PROCEDURE. Patients will undergo Fredet-Ramstedt pyloromyotomy or Heineke-Mickulicz pyloroplasty. The pyloromyotomy involves dividing the serosal and muscular layers over the anterior surface of the pylorus for a distance of approximately 4 cm and can be completed in 5 to 10 minutes. A pyloroplasty, on the other hand, involves making a full-thickness longitudinal incision through the anterior wall of the pylorus and proximal duodenum and reapproximating the edges in a transverse fashion using a one- or two-layer closure. The latter procedure takes 15 to 20 minutes to perform. Complications associated with the procedure may be technical (ie, leakage from the drainage site, abscess) or mechanical (ie, dumping syndrome, duodenogastric reflux).

VARIABLES AND PROBABILITIES. Table 1 summarizes the variables and estimates of their values that will be used in the decision analysis; these values are based on critical review of the available literature. The incidence of symptomatic gastric outlet obstruction after esophagectomy or esophagogastrectomy has been variously estimated to be between 10% and 24% [2, 12]. We have chosen an incidence of gastric outlet obstruction of 14%. A randomized clinical trial of drainage versus no drainage by Cheung and associates [2] found the incidence of gastric outlet obstruction without drainage to be 14% (3/21). The effectiveness of the drainage procedure in preventing symptomatic gastric outlet obstruction was 100% in the same randomized clinical trial [2]. For the decision analysis, we will consider the drainage procedure to be 95% effective.

Complications associated with the addition of a drainage procedure to esophagectomy or esophagogastrectomy can be categorized as technical or mechanical, as already mentioned. The randomized trial by Cheung and associates [2] found the technical complication rate of pyloroplasty to be zero but did not objectively assess the incidence of duodenogastric reflux. Cheung and associates stated that the incidence of dumping was 10% in their series. We will use a drainage-associated complication rate of 10% in the analysis.

Estimates of the test's sensitivity (0.75) and specificity (0.50) are conservative because the test is unproved. A

Table 1. Variables in Decision Tree

Variable	Estimate (%)
Pretest likelihood of gastric outlet obstruction (C)	14
Effectiveness of drainage procedure (e)	95
Probability of drainage-associated complication (c)	10
Sensitivity of the test (sens)	75
Specificity of the test (spec)	50

two-way sensitivity threshold analysis approach will be used to ascertain the sensitivity and specificity required of a test to make it a worthwhile strategy upon which to base treatment.

UTILITIES. To quantify the value that individuals place on each of these health states, we use the concept of utility. This numerical method captures the preferences of individuals for these health states, based on utility theory. This theory bases rational decision making on a number of axioms that describe how individuals ought to behave when faced with decision making under uncertainty [13]. Each of the health states at the terminal nodes are thus assigned a utility value that quantifies preferences for these states. In the context of the present decision tree, the relative utility of each outcome is compared with the optimal outcome (no complication), which is assigned a utility of 1.0. The utilities used in the analysis are presented in Table 2. The utility of a patient having gastric outlet obstruction has been assigned a value of 0.0 because this is the complication that surgeons are trying to eliminate by performing a drainage procedure at the time of initial esophageal resection. The utility of a patient experiencing a complication related to the drainage procedure has been somewhat arbitrarily assigned a value of 0.7 as the complication rate and severity of a complication when it does occur is less morbid.

Analytic Strategies

BASELINE ANALYSIS. Using the decision analysis computer software "SMLTREE," analyses were conducted using baseline values listed in Table 1. The expected utility of a particular branch is a weighted average of the utility associated with all possible outcomes of that branch. For example, the drain none branch in Figure 1 is associated with two possible outcomes, gastric outlet obstruction and no gastric outlet obstruction. The expected utility of gastric outlet obstruction is determined by multiplying the rate times the utility ($0.14 \times 0 = 0.0$), and the expected utility of no obstruction is determined by multiplying the rate times its utility ($0.86 \times 1.0 = 0.86$). Using SMLTREE we can determine the strategy that will yield the greatest expected utility by a procedure referred to as folding back.

SENSITIVITY "THRESHOLD" ANALYSIS. The effect that changes in baseline variables have on the expected utility of each branch is studied by conducting a series of sensitivity analyses. The threshold point in clinical decision making is defined as the point where two different approaches to managing a patient appear to have the same potential value (eg, are expected to result in equal complication rates) and therefore the clinician is indifferent about choosing either of the two strategies [14]. There are two possible thresholds: a "testing threshold" where the decision is made between draining no one or draining only high-risk patients, and a "test–drain all threshold" where the decision is made between draining only high-risk patients or draining all patients. To determine the threshold values of pretest likelihood of gastric outlet obstruction (C) and effectiveness of the drainage procedure (e) (the two variables that we believe will vary according to clinical circumstances) that will make clinicians indifferent to the choice of strategies, we plug the baseline values assumed for all of the variables (except C and e) into the three expressions for the expected total hospital complication rate associated with each strategy (see Fig 1). We then set two of the three expressions equal to each other (ie, drain none = test, test = drain all), which results in an equation and two variables: C and e. This is referred to as a two-way sensitivity or threshold analysis. It shows us how sensitive the choice of strategy is to simultaneous variations in the two variables (C and e).

Table 2. Utilities in the Decision Tree

Utility Name	Utility
No complication	1.0
Drainage-associated complication	0.7
Gastric outlet complication	0.0

Table 3. Result of Decision Tree

Expected Utility	Value
Drain all	0.96321
Drain none	0.86000
Test	0.94386
Expected utility (choose) Choose: drain all	0.96321

Results

The result of the decision analysis is presented in Table 3. A drain all policy has the highest expected utility (0.96321) using the baseline variables in Table 1 and is thus the preferred approach.

One-way sensitivity analysis (Fig 2) indicates that a drain all policy is appropriate if the incidence of gastric outlet obstruction is greater than 10%, keeping all other variables constant. Figure 3 graphs a one-way sensitivity analysis, illustrating that as long as the effectiveness of the drainage procedure exceeds 40%, keeping all other variables constant, a drain all policy is once again favored.

Figure 4 plots the test threshold and test–drain all threshold allowing the incidence of gastric outlet obstruction and the effectiveness of the drainage procedure to vary from 0% to 100%. Clearly, for clinicians facing an incidence of gastric outlet obstruction greater than 10%, a drain all policy is appropriate if the drainage procedure works 95% of the time. A test would be useful if the drainage procedure were only 20% to 60% effective in averting gastric outlet obstruction in the setting where its anticipated incidence was between 10% and 20%.

Figure 5 plots the test–drain all sensitivity threshold across the entire range of specificities. To be helpful, the test would need to remain at least 80% sensitive even if it were 100% specific. If the sensitivity was 0.6, for example, a drain all policy would be appropriate through the entire

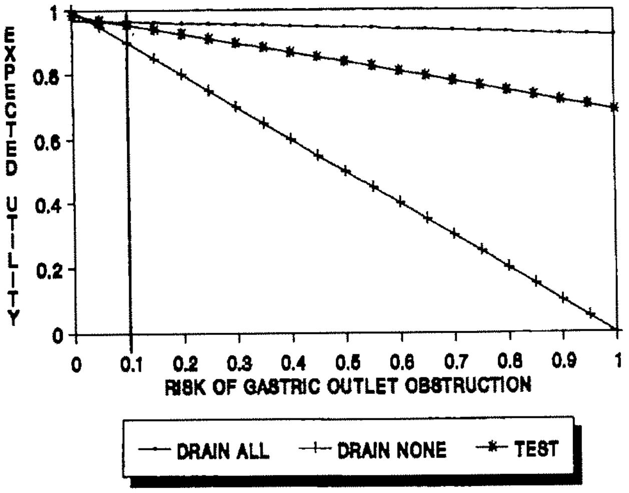

Fig 2. One-way sensitivity analysis of the incidence of gastric outlet obstruction versus its expected utility for each treatment strategy.

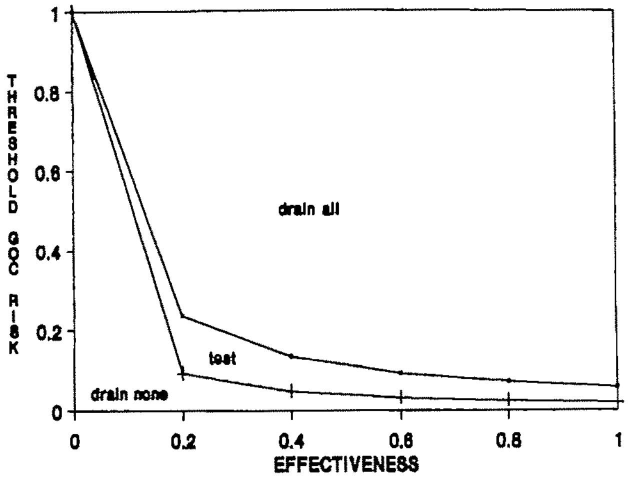

Fig 4. Two-way sensitivity analysis varying the effectiveness of the drainage procedure against the incidence of gastric outlet obstruction (GOC).

range of possible specificities. To date, no test has been assessed with regard to its ability to predict risk of postoperative gastric outlet obstruction. The wide range of clinical management of this problem and the absence of reasonable criteria for adopting a policy on gastric drainage suggest that the likelihood of such a test being developed is small.

Comment

This decision analysis represents an attempt to assess the relative merits of draining the intrathoracic stomach in patients undergoing esophagectomy. Although a randomized clinical trial [2] has addressed this question in the past, the number of patients randomized was too small for any definitive conclusion to be made. Despite its methodological shortcomings, the trial [2] did advocate a drain all policy. A multicentered randomized clinical trial approach would be necessary to answer this question conclusively, however, because no one center could be expected to accumulate enough experience within a reasonable time period. Another approach to the question involves decision analysis.

The analysis presented in this article demonstrates that with an incidence of gastric outlet obstruction of 14% and a drainage procedure that is 95% effective, a drain all policy is the most appropriate.

The two-way sensitivity analysis presented in Figure 4 demonstrates that a drain all policy should apply in most clinical settings. Allowing the incidence of gastric outlet obstruction and the effectiveness of the drainage proce-

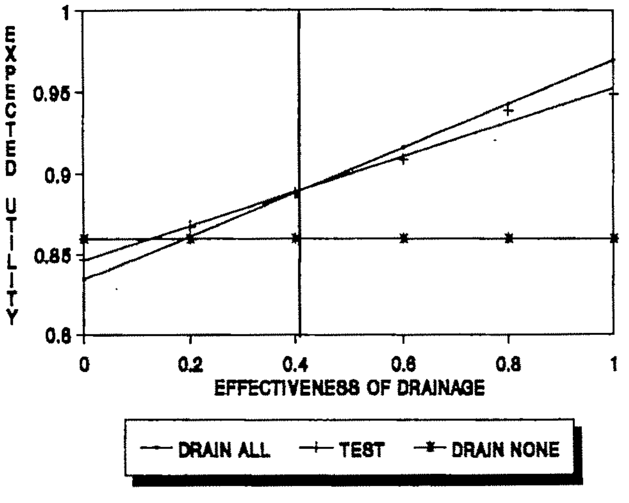

Fig 3. One-way sensitivity analysis of the effectiveness of drainage versus its expected utility for each treatment strategy.

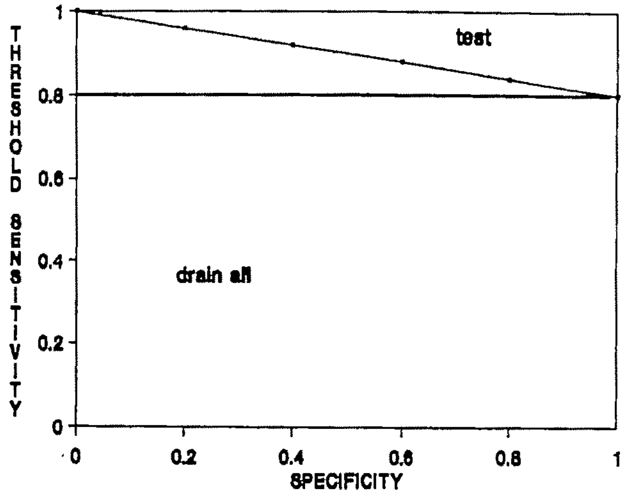

Fig 5. Two-way sensitivity analysis of the specificity versus sensitivity for the test. The line represents the test–drain all threshold.

dure to vary between 0% and 100% permits clinicians to decide which approach fits their situation. A test would be considered appropriate for clinical situations where both the incidence of gastric outlet obstruction is less than 10% and the effectiveness of the drainage procedure ranges between 20% and 60%. This is represented by the area entitled *test* in Figure 4. It can be seen from this figure that the area entitled *drain all* encompasses the majority of clinical scenarios likely to be encountered in clinical practice.

The two-way sensitivity analysis presented in Figure 5 demonstrates that given an incidence of obstruction of 14%, an effectiveness of drainage of 95%, and a drainage-associated complication rate of 10%, if a test were to be developed with the aim of placing patients into high- and low-risk groups it would require a sensitivity of at least 80% even if it was 100% specific. It is unlikely that the test could be this accurate. Although a test seems rational, the analysis presented here indicates that it would be very difficult to devise a test that would be useful for patient stratification.

If the probabilities used in this analysis reflect those at your institution, then consideration should be given to performing a drainage procedure in all patients undergoing esophagogastrectomy.

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Appendix 1. Test for Risk of Postoperative Gastric Outlet Obstruction[a]

History, physical examination	
Peptic ulcer disease	
Suspected	+1
Proven (roentgenogram, endoscopy)	+2
Symptoms of early satiety or bloating	+1
Coexisting disease	
Diabetes	+1
Connective tissue disease	+1
UGI series: demonstration of	
Duodenal bulb deformity	+2
Duodenal ulcer	+2
Pyloric channel narrowing	+2
Gastric dilatation	+1
Retained food	+1
Radionuclide study: delayed gastric emptying	+2
Endoscopy: demonstration of	
Duodenal scarring/fibrosis	+2
Peptic ulcer	+2
Tight pylorus	+2
Gastritis/duodenitis	+1
Intraoperative: demonstration of	
Duodenal scarring	+2
Pyloric hypertrophy	+2

[a] Scoring of the test: any +2 or combination of two +1's is considered a positive test

One-Stage Operation for Synchronous Primary Cancers of the Lung and the Trachea

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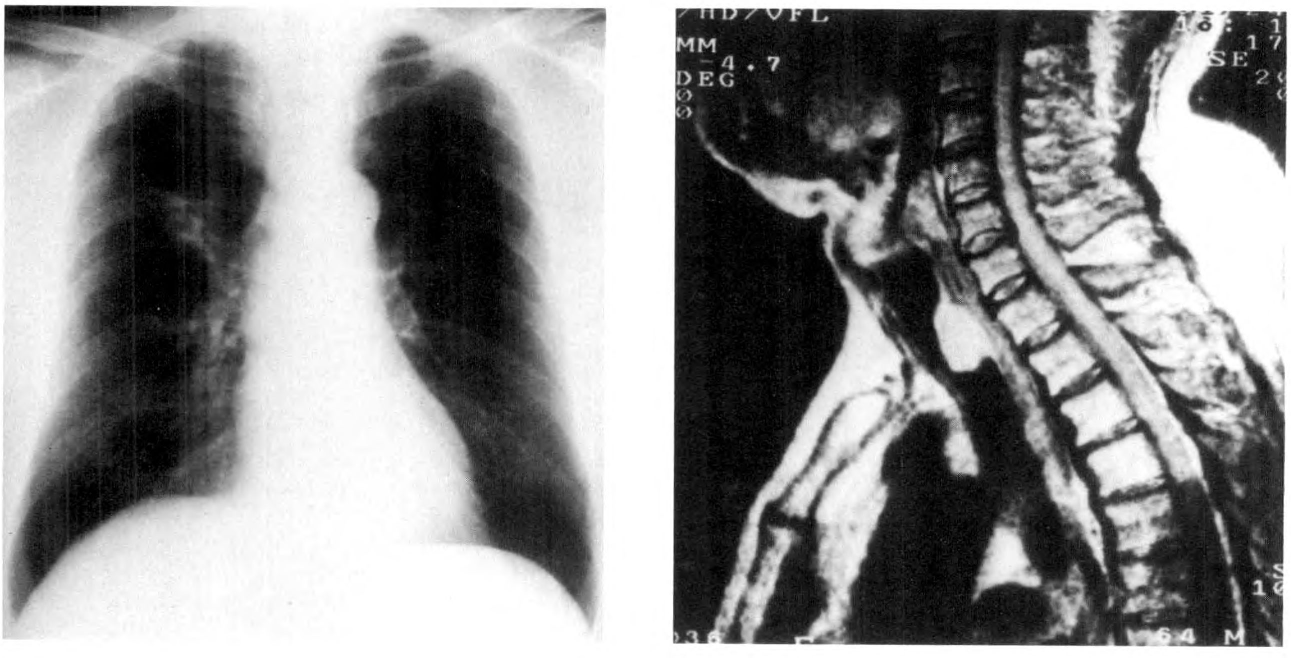
A rare combination of synchronous primary adenocarcinoma of the right upper lobe of the lung and adenoid cystic carcinoma of the subglottic trachea was simultaneously managed by lobectomy with lymph node dissection and sleeve resection of the upper trachea through median sternotomy and cervical collar incisions. This combined approach should be a perfectly acceptable one for synchronous tumors of the proximal trachea and of the right upper and middle lobes and left upper lobe of the lung.

(Ann Thorac Surg 1992;53:498–500)

We describe a rare case of synchronous primary adenocarcinoma of the right upper lobe of the lung and adenoid cystic carcinoma of the subglottic trachea, which was successfully treated by one-stage operation.

A 64-year-old man, who had been a heavy smoker for 40 years, was admitted with a 6-month history of dry cough. A chest roentgenogram showed a tumor shadow of the right upper lobe with no evidence of a tracheal tumor (Fig 1A). At bronchoscopy, a large tumor with a smooth surface was found on the membranous portion of the trachea, 2.5 cm below the vocal cords, occupying two thirds of the lumen of the subglottic trachea. Biopsy specimens showed adenocarcinoma of the right upper



A

B

Fig 1. (A) Chest roentgenogram showing a tumor of the right upper lobe. (B) Magnetic resonance image showing a tumor of the membranous portion of the subglottic trachea.

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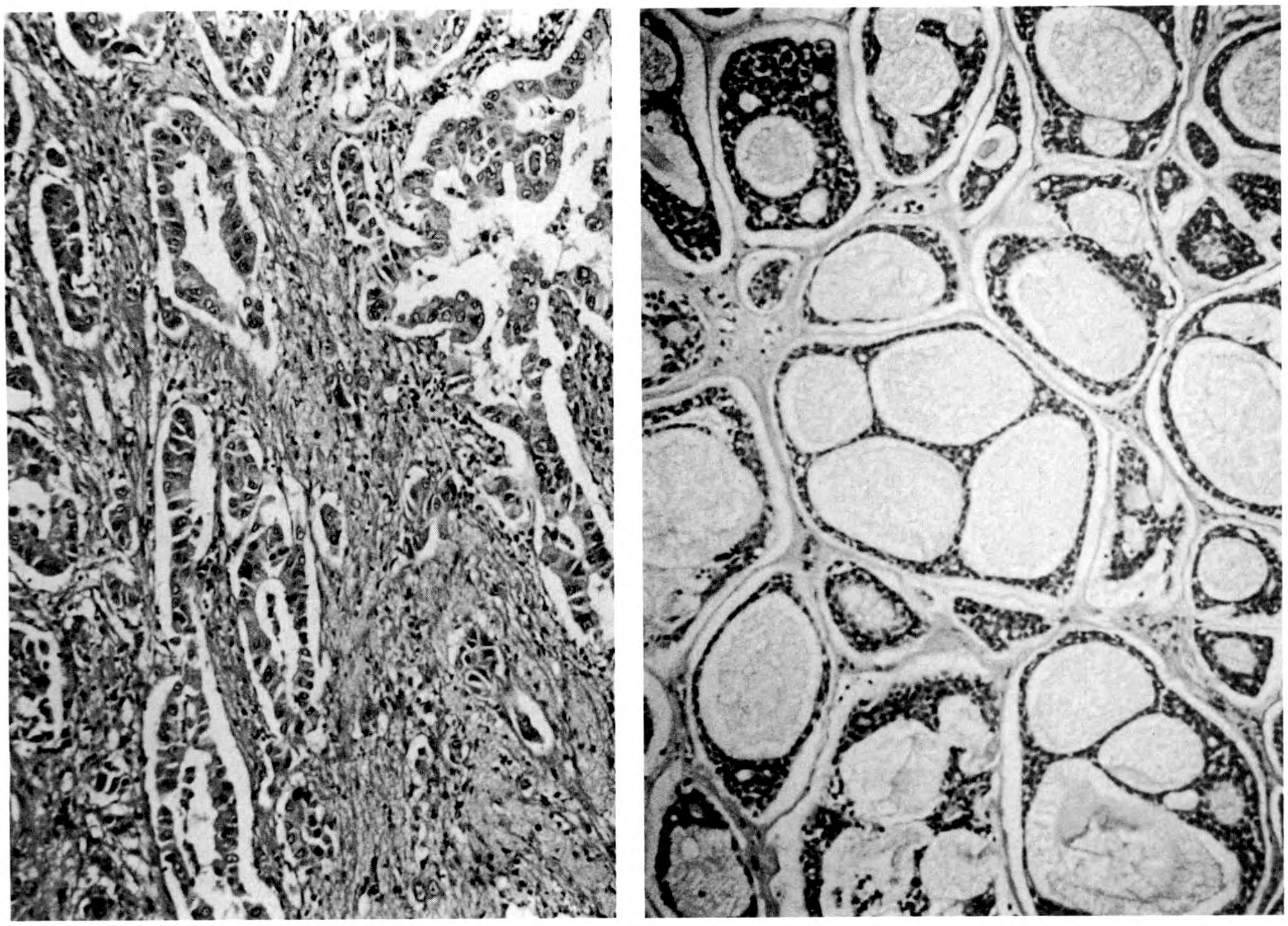

Fig 2. (A) Adenocarcinoma of the lung. (Hematoxylin and eosin, ×100 before 1% reduction.) (B) Adenoid cystic carcinoma of the trachea. (Hematoxylin and eosin, ×100 before 1% reduction.)

lobe and adenoid cystic carcinoma of the trachea. Magnetic resonance imaging (Fig 1B) demonstrated a tumor of the membranous portion of the subglottic trachea measuring 2.5 × 2 cm. The tumor penetrated the posterior membranous wall to reach the esophagus, and there was submucosal invasion to the posterior wall of the cricoid cartilage. Gallium and bone scintigrams were negative for metastasis. One-stage operation through median sternotomy and cervical collar incisions was indicated based mainly on the locations of both tumors.

On February 3, 1989, under general anesthesia with oral intubation using a 7.5-mm endotracheal tube beyond the tracheal tumor, operation was performed through a median sternotomy and a cervical collar incision. Right upper lobe lobectomy was first performed, followed by mobilization of the mediastinal trachea and right and left main bronchi during mediastinal lymph node dissection. The pulmonary ligament was dissected on the right side. The cervical trachea was dissected, keeping close to the trachea with special care taken not to damage the recurrent laryngeal nerves. The tumor penetrated the membranous wall and was adherent to the esophagus, which was easily dissected free. Respiration was maintained through an endotracheal tube inserted into the distal trachea from the operative field, and sleeve resection of the cervical trachea from just below the cricoid cartilage to the upper margin of the sixth cartilage was performed, sparing the anterior part of the first tracheal ring. Frozen section of the proximal margin revealed mucosal invasion by tumor cells; therefore, the mucosa of the posterior wall of the cricoid cartilage was cut back to within a short distance of the arytenoid cartilage. The vocal cords and anterior part of the first tracheal cartilage were preserved. After cervical flexion, the mediastinal trachea was mobilized superiorly, and the flap of membranous wall of the trachea was fitted into the defect of the posterior part of the cricoid cartilage to provide mucosal coverage [1]. An end-to-end anastomosis was performed with interrupted 3-0 absorbable sutures. To minimize tension on the anastomosis, the patient's chin was sutured to the presternal skin to maintain cervical flexion for 2 weeks postoperatively. The patient was extubated on the first postoperative day, and there was no evidence of recurrent laryngeal nerve palsy. He received a course of 50 Gy of radiation to the upper mediastinum and trachea. Bronchoscopy performed before discharge revealed good healing of the tracheal anastomosis without stenosis, and he was followed up as an outpatient.

Microscopic examination demonstrated a well-differentiated papillary adenocarcinoma of the lung (Fig 2A) with mediastinal lymph node metastasis (T1 N2 M0; stage IIIa) and a cribriform-type adenoid cystic carcinoma of the trachea, in which tumor cells were arranged in nests and oval shapes (Fig 2B). Lymphatic metastasis was not observed for the adenoid cystic carcinoma.

Comment

The occurrence of multiple primary malignant tumors has increased due to improvements in therapy for the initial primary malignant tumor, resulting in a longer survival time. The incidence of multiple primary cancers has been reported as 5.3% [2] in an autopsy series of cases of malignant disease. Lung cancer is one of the most common tumors in reported multiple series, and 10% of lung cancer patients had a second primary malignant tumor [2]. Primary tracheal carcinoma, however, is an uncommon entity, with an incidence of 1 in 15,000 to 20,000 autopsy cases or 1 in 1,000 patients with carcinoma [3]. Adenoid cystic carcinoma and squamous cell carcinoma are described as occupying 40% and 36% of the tracheal tumors, respectively, in a recent large series [4]. The histology of adenoid cystic carcinoma of the trachea is characterized by cords and sheets of fairly uniform small cells and cystlike structures of various size [5].

Primary malignant tumors of the trachea are well known to be preceded or followed by carcinoma of the lung [4, 5]. The present case of synchronously occurring adenoid cystic carcinoma of the trachea and adenocarcinoma of the lung precisely fits the criteria for multiple primary carcinomas described by Warren and Gates [6]. An asymptomatic proximal tracheal tumor might have been missed if flexible bronchoscopy had been used after the patient was intubated. One should perform careful bronchoscopy in all patients with malignant tumors of the lung and the trachea because of the possibility of synchronous primary cancers.

A median sternotomy incision is ordinarily applied for lung cancer in our institute, according to the procedures of operation (ie, lobectomy of the right upper and middle lobes and left upper lobe with lymph node dissection), because of the technical feasibility. We can also apply it to poor-risk patients (ie, those with advanced age or compromised pulmonary function) because of lesser respiratory restraint than a standard thoracotomy, due to not incising the respiratory muscles and much less wound pain. One-stage operation for the present patient was performed through median sternotomy and cervical collar incisions, which provided extremely good access to the entire trachea and right upper lobe of the lung at the same time. Mobilization of the mediastinal trachea and both main bronchi could be easily performed during mediastinal lymph node dissection, allowing sufficient reduction of tension on the tracheal anastomosis. This combined approach should be a perfectly acceptable one for synchronous tumors of the proximal trachea and of the right upper and middle lobes and left upper lobes of the lung.

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Isolation of the Right Subclavian Artery

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Loss of continuity between subclavian artery and aorta with persistent connection to the homolateral pulmonary artery through a ductus arteriosus is an uncommon malformation, involving generally the left subclavian artery and associated with intracardiac or aortic arch anomalies. We report a case of right subclavian isolation with a left-sided aortic arch, presenting as a single anomaly and surgically corrected by aortic reimplantation.

(Ann Thorac Surg 1992;53:501–3)

Complete disconnection of a subclavian artery from aortic arch, named *isolation* in 1964 by Stewart and associates [1], is an uncommon malformation of the aortic arch system, defined as a loss of continuity between one subclavian artery and aorta with persistent connection to the homolateral pulmonary artery through a patent or nonpatent ductus arteriosus. This subclavian isolation is always observed on the side contralateral to the position of the aortic arch but is well-known as involving the left subclavian artery four times more frequently than the right one [2]. In most, if not all, reported cases (most of which were diagnosed at autopsy), subclavian isolation was associated with intracardiac (ventricular septal defect or tetralogy of Fallot) or aortic arch (right or interrupted aortic arch or bilateral ductus) anomalies.

A 3-year-old boy was referred because of a continuous cardiac murmur, grade 2/6 in intensity, discovered during routine examination. It was heard in the third right intercostal space, radiating to the second right and left intercostal spaces and to the back. Both radial pulses were described as identical, but blood pressures, measured by the cuff method, were 61/42 mm Hg in the right arm and 92/40 mm Hg in the left one. There was no other clinical sign at physical examination.

Chest roentgenogram showed a left-sided aortic arch, and the electrocardiogram was normal. The only abnormality identified on Doppler echocardiography was a systolodiastolic flow in the main pulmonary artery suggesting a patent ductus arteriosus. At cardiac catheterization, right heart pressures were normal, but a left-to-right shunt was confirmed by the increase in oxygen saturation at the pulmonary arterial level. Pulmonary artery angiographic results were normal but, when the contrast medium returned to the left heart and to the left-sided aortic arch, the first branch vessel was the right carotid artery rather than a brachiocephalic artery. A thoracic cineangioaortogram showed absence of either normal or aberrant retroesophageal right subclavian artery and also showed, at the isthmus level, a small blind diverticulum representing insertion of ligamentum arteriosum. A delayed view visualized a descending right subclavian artery opacifying the pulmonary arterial system and suggesting a subclavian steal (Fig 1). Selective opacification of a tortuous, collateral, deep vessel was then obtained from the descending aorta (Fig 2), filling the subclavian artery toward the right pulmonary artery. At last, direct opacification of this right subclavian artery was achieved after selective catheterization of a right patent ductus implanted on the right pulmonary artery (Fig 3), confirming the diagnosis of isolation of the right subclavian artery from aorta with left-sided aortic arch, right patent ductus arteriosus, and left ligamentum arteriosum without associated anomalies.

On February 22, 1990, the child underwent surgical repair of this anomaly through a median sternotomy. The aberrant subclavian artery was located between the superior vena cava and aorta and was connected to the initial part of the right pulmonary artery. It was divided at its distal level and its pulmonary stump was oversewn; after proper resection, the subclavian artery was directly reimplanted into the ascending aorta with 7-0 Prolene (Ethicon, Somerville, NJ) interrupted stitches. Six months postoperatively, blood pressure measurements were identical and normal in both arms and a control aortography showed a satisfactory result (Fig 4).

Comment

The term *isolation*, introduced by Stewart and associates [1], described "a left aortic arch from which the right subclavian artery has become completely disconnected" with "apparently a strong tendency for the right ductus arteriosus to remain intact and anchor the right subclavian artery proximally to the right pulmonary artery." This only case reported [1] was classified as subgroup II C2. Edwards' widely accepted embryologic model of malformation of the aortic arch system [3] would explain this right subclavian isolation by interruption of the right aortic arch at two locations: (1) dorsal to the right subcla-

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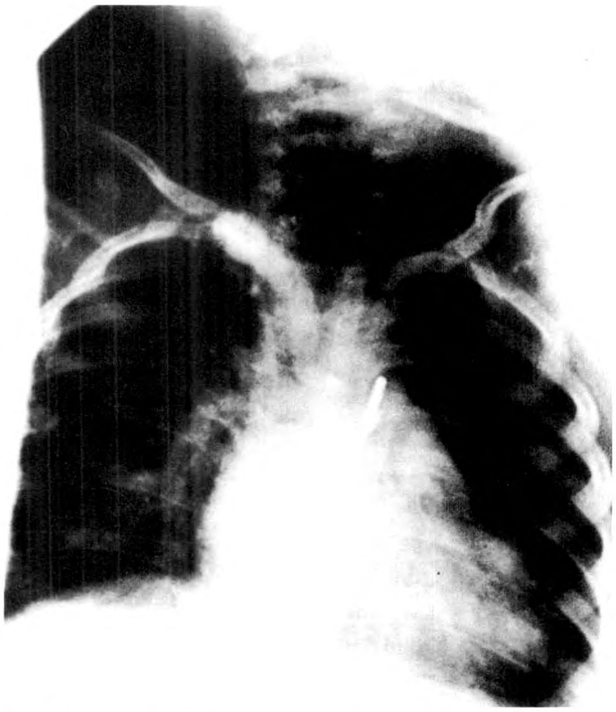


Fig 1. Delayed view from aortic arch injection shows retrograde filling of an isolated right subclavian artery.

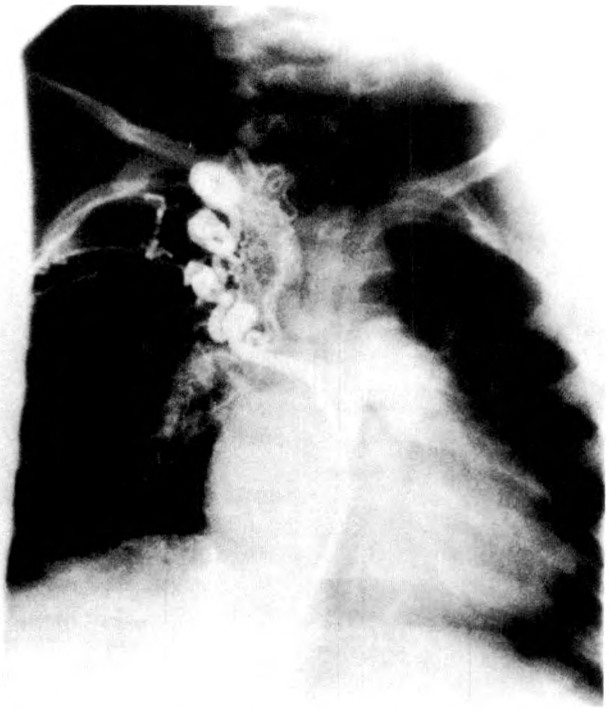


Fig 2. Selective opacification, from descending aorta, of a tortuous collateral vessel filling the right subclavian artery.

vian artery and ductus-arch junction and (2) between the right common carotid artery and the right subclavian artery (Fig 5). Isolation of the left subclavian artery is by far more frequent than right subclavian isolation, of which 7 cases have been reported in literature: by Barger and co-workers [4] (1 case), Stewart and associates [1] (1 case), Nath and colleagues [5] (3 cases), Brill and associates [6], and Mathieson and co-workers [7] (1 case); all these patients had associated severe intracardiac malformations. The case described here is the eighth reported case of a right subclavian isolation, and it is extremely unusual in that it was seen as an isolated anomaly.

This isolated artery is generally supplied by collaterals originating principally in the contralateral subclavian artery. Among them are the vertebral arteries, in which countercurrent flow implies hemodynamical if not cere-

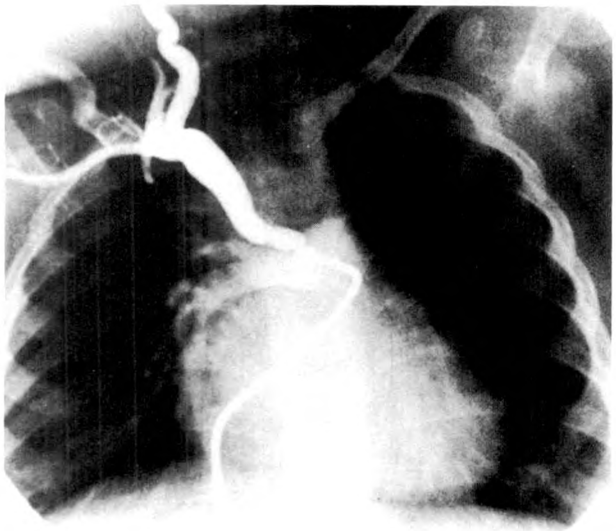


Fig 3. Selective opacification of the isolated right subclavian artery from the right pulmonary artery.

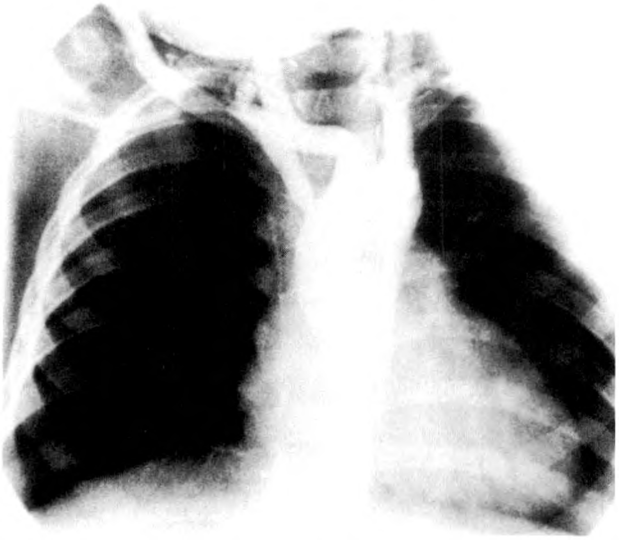
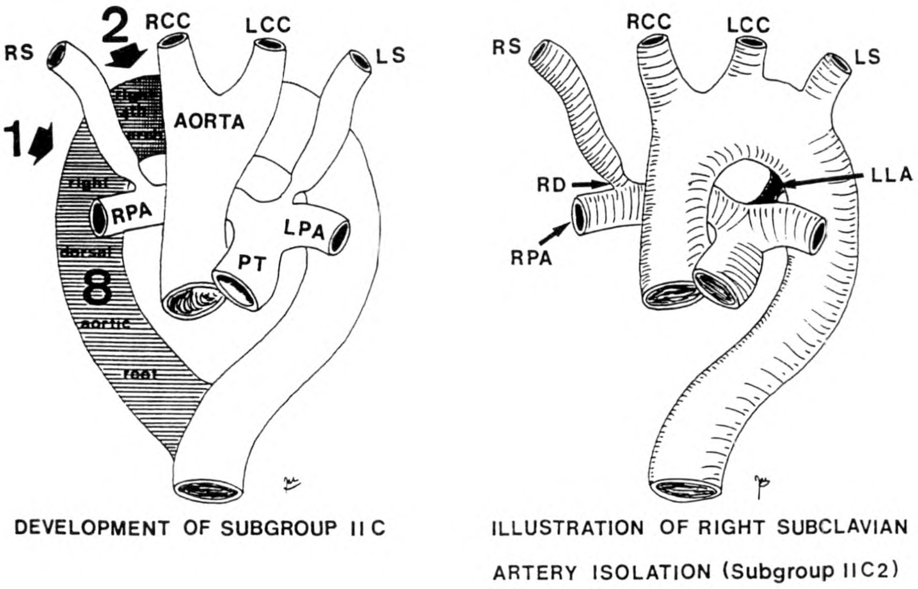


Fig 4. Postoperative aortogram showing antegrade filling of the reimplanted right subclavian artery.



DEVELOPMENT OF SUBGROUP II C

ILLUSTRATION OF RIGHT SUBCLAVIAN ARTERY ISOLATION (Subgroup IIC2)

Fig 5. Diagram adapted from Edwards' embryologic model of aortic arch system. Shaded areas *represent sites of interruption for development of right subclavian artery isolation:* 1 *(right dorsal aortic root = 8) and* 2 *(right fourth arch).* (LCC *and* RCC *= left and right common carotid artery;* LLA *= left ligamentum arteriosum;* LPA *and* RPA *= left and right pulmonary artery;* LS *and* RS *= left and right subclavian artery;* PT *= pulmonary trunk;* RD *= right patent ductus arteriosus.)*

bral symptoms of a subclavian steal syndrome; however, these cerebral symptoms are quite uncommon in children, who never exhibit a vertebrobasilar syndrome despite identical arrangement after a Blalock-Taussig shunt or a subclavian flap repair of coarctation (Waldhausen's technique). In fact, if the ductus connecting the isolated subclavian artery to pulmonary artery is closed, the subclavian steal is limited. If the ductus is patent, all depends on the pulmonary arterial pressure; in patients such as ours with normal pulmonary arterial pressure, the subclavian steal, assessed by the left-to-right shunt, sets the potential for cerebral symptoms. In patients with pulmonary arterial hypertension due to a serious associated left-to-right shunt (ventricular septal defect or large contralateral ductus with elevated pulmonary vascular resistances), a right-to-left shunt may occur through the ductus into the isolated subclavian artery [5], with subsequent cyanosis in the arm. When isolated, isolation of the subclavian artery may present as a left-to-right shunt; although this condition may be clinically asymptomatic, it should be surgically corrected to prevent symptomatic subclavian steal at adult age. But when it is associated with intracardiac malformation, especially those with reduced pulmonary blood flow such as tetralogy of Fallot [8, 9], it is of major importance to identify this anomaly before considering a Blalock-Taussig shunt, because this anastomosis is usually performed on the opposite side of the aortic arch.

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Left Ventricular Pseudoaneurysm Associated With Mitral Regurgitation

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A patient with a large posterolateral left ventricular pseudoaneurysm flush with the posterior papillary muscle and associated with mitral regurgitation was successfully treated surgically. The operation consisted of opening the sac of the aneurysm, dissecting the wall of the left ventricle from the fibrous wall of the sac, leaving a cuff of fibrous tissue suitable to hold sutures, and closing the defect with a Dacron patch.

(Ann Thorac Surg 1992;53:504–6)

A left ventricular pseudoaneurysm develops after acute rupture of an infarcted area of the left ventricle. Such ruptures are usually fatal, but when the pericardium is sufficiently adherent to the epicardium, the rupture may result in a localized hemopericardium. The persistent communication of the hemopericardium with the left ventricular cavity results in gradual expansion of the hemopericardium into a large false aneurysm, the wall of which is composed of pericardium and adhesions and the mouth of which is usually narrow. Such aneurysms have a strong tendency to rupture, and therefore surgical resection with or without coronary revascularization is usually advisable [1]. This is in contrast to true left ventricular aneurysms, in which the risk of rupture is very rare; therefore, the presence of a true left ventricular aneurysm per se is not considered an indication for operation.

A 60-year-old man who was a heavy cigarette smoker and had chronic bronchitis and a history of hypertension was urgently hospitalized on July 1, 1990, with supraventricular tachycardia, severe systemic hypertension (200/110 mm Hg), and acute pulmonary edema. An urgent medical treatment in the coronary care unit succeeded in controlling the situation. An echocardiographic study done on the same day showed a localized pericardial effusion below the left ventricle.

On July 4, 1990, the general condition deteriorated again, dyspnea increased, and orthopnea developed. A chest roentgenogram showed evidence of pulmonary congestion and a huge cardiomegaly. Electrocardiography showed nonspecific ST segment and T wave changes opposite to the lateral wall of the left ventricle. Doppler echocardiography showed a large cavity containing fluid communicating with the left ventricle and compressing the left atrium. The diagnosis of a false aneurysm of the left ventricle was considered.

The patient was transferred from Algeria to Paris and arrived at our hospital on July 12, 1990. An echocardiographic study (Figs 1, 2) confirmed the presence of a large false aneurysm (6 cm × 3 cm) situated posterolateral to the left ventricle and communicating with the left ventricular cavity. The mouth of the false aneurysm was between the posterior papillary muscle and the ring of the mitral valve. Left ventriculography showed a large posterolateral sac that communicated freely with the cavity of the left ventricle. The anterior wall of the left ventricle and the interventricular septum moved normally, whereas the posterior wall showed marked hypokinesia. There was mild to moderate mitral insufficiency. Coronary angiography showed a normal left anterior descending coronary artery system and normal right coronary artery system, whereas the main circumflex artery was totally occluded after giving off a long, high lateral branch.

The patient was scheduled for an urgent operation for resection of this aneurysm. The left femoral artery was exposed "just in case" but not cannulated. Median sternotomy was done safely, and cardiopulmonary bypass was established as usual through the ascending aorta and the two venae cavae. A left ventricular vent was put through the right superior pulmonary vein. Myocardial protection was afforded by cold crystalloid cardioplegia supplemented by moderate hypothermia and topical cooling.

Dissection of intrapericardial adhesions over the left ventricle allowed the visualization of a large sac about 10 cm in diameter situated posterolateral to the left ventricle. The sac was opened and found devoid of any thrombi or blood clots and freely communicating with the cavity of the left ventricle through a big oval hole about 3 cm × 2 cm situated lateral to and flush with the posterior papillary muscle of the left ventricle. The posterior papillary muscle and its chordae were well exposed through the defect (Fig 3).

There were two choices as regards the method of

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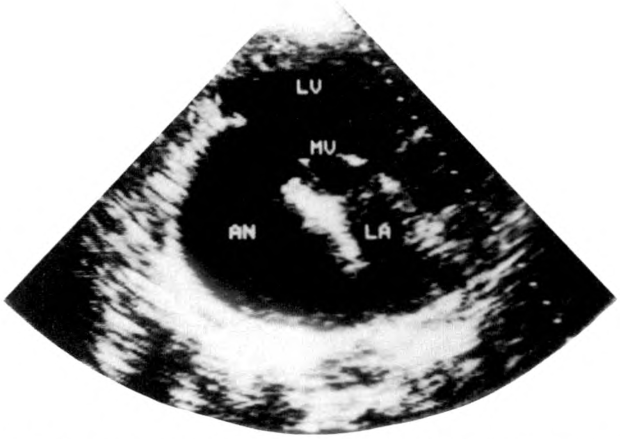

Fig 1. Two-dimensional echocardiographic picture showing the aneurysm (AN) compressing the left atrium (LA) and communicating freely with the left ventricular cavity (LV) by a wide orifice. (MV = mitral valve.)

closure of this defect, either to close it directly with the risk of changing the papillary muscle-chordal axis of the mitral valve and aggravating the degree of mitral incompetence or to close it with a patch, which will form a relatively big akinetic area. We preferred the second choice, and a patch of Dacron (4 cm × 3 cm) was used and sutured in place by a series of interrupted sutures of 4-0 Prolene with Teflon pledgets and reinforced by another layer of continuous suture of 4-0 Prolene. Weaning from bypass necessitated the use of intraaortic balloon counterpulsation and dobutamine hydrochloride (Dobutrex; Eli Lilly and Co, Indianapolis, IN). Hemostasis was difficult as there was bleeding from the wall of the false aneurysm.

In the intensive care unit the patient was in excellent hemodynamic condition with a cardiac index of 3 $L \cdot min^{-1} \cdot m^{-2}$ on the balloon counterpulsation and the dobutamine. Continuous bleeding persisted throughout the first night but it did not affect the hemodynamic status of the patient.

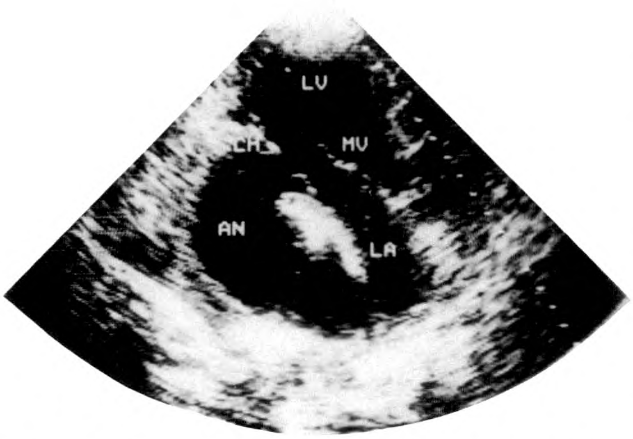

Fig 2. Echocardiographic picture showing the close relationship of the posterior papillary muscle and chordae (CH) of the mitral valve (MV) with the mouth of the aneurysm (AN). (LA = left atrium; LV = left ventricle.)

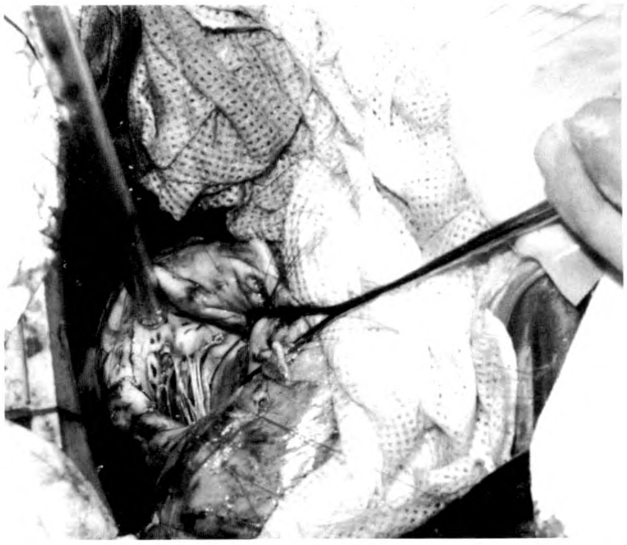

Fig 3. Operative picture showing the wide orifice of the aneurysm and the close relationship with the mitral valve apparatus.

The next morning, the patient was reopened and we found that bleeding came from the posterior aspect of the left ventricle from a solitary point at the suture line of the patch. This was not accessible without the use of extracorporeal circulation. Two interrupted sutures of Prolene with Teflon pledgets succeeded in stopping the bleeding. The patient was weaned again from bypass by balloon counterpulsation and dobutamine. In the intensive care unit the patient's condition was excellent both hemodynamically and hemostatically. Two days later the patient was extubated with a good hemodynamic profile without the balloon and the inotropic support. On the fifth day, the patient was transferred from the intensive care unit to the ward, and 2 weeks later he went back to Algeria in good condition.

Comment

This large pseudoaneurysm with its thick fibrous wall cannot develop in a 2-week period. We believe that there was an old attack of myocardial infarction that passed smoothly and resulted in the formation of such a huge aneurysm. Probably the acute pulmonary edema that had occurred on July 1 resulted from the rhythm disturbance and the hypertension.

The mild to moderate degree of mitral regurgitation that was present preoperatively was probably of an ischemic nature, but another important mechanism in this case was the lack of proper shortening of the longitudinal axis of the left ventricle during systole due to the discontinuity of the outer longitudinal muscle layer of the left ventricle over a big area that corresponds to the defect and the close proximity between the defect and the posterior papillary muscle.

We found no increase in the degree of mitral regurgitation after operation, and we believe that our choice of closing the defect by using a patch was correct as the other choice of direct closure of the defect by edge to edge probably would aggravate the degree of mitral regurgitation. We also believe that a concomitant mitral valve procedure, as described in other reports [2], increases hospital mortality.

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The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas, TX, on February 7, 1993. The closing date for registration is August 1, 1992.

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Invasive Thymoma With Intracaval Growth Into the Right Atrium

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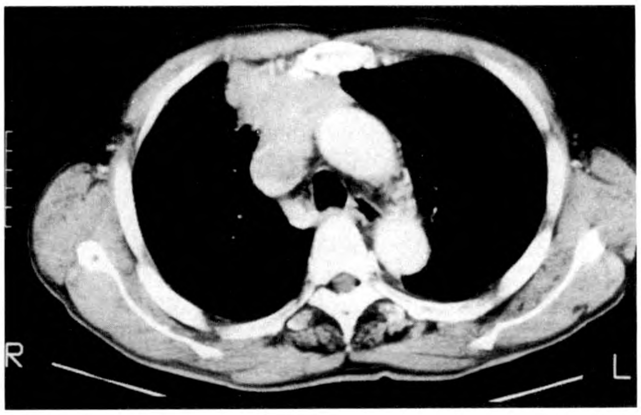
We report an unusual case of invasive thymoma with intracaval growth into the right atrium. Computed tomography and venacavography demonstrated this manner of extension of thymoma. The tumor was completely removed by means of cardiopulmonary bypass after four courses of chemotherapy. Multidisciplinary treatment for invasive thymoma with this growth pattern is thought to be useful.

(Ann Thorac Surg 1992;53:507–9)

A 72-year-old man was referred to the Tochigi Cancer Center on February 7, 1989, complaining of swelling of the face and exertional dyspnea. Chest roentgenogram showed a mass in the anterior mediastinum and enlargement of the cardiac shadow. Computed tomographic scans (Fig 1) revealed pericardial effusion and a large anterior mediastinal mass infiltrating the superior vena cava (SVC) and the pericardium. Superior venacavography (Fig 2) revealed that the mass formed a tumor thrombus measuring 15.5 × 3.4 cm extending into the SVC and the right atrium. Histologic findings of the specimen obtained by percutaneous needle biopsy were compatible with those of thymoma of predominantly lymphocytic type.

Because the tumor was considered unresectable and a pulmonary embolism or distant metastasis would be prevented, the patient was treated by primary chemotherapy consisting of cisplatin (20 mg $\cdot$ m^{-2} $\cdot$ day^{-1} continuous 24-hour infusion on days 1 through 4), doxorubicin (40 mg $\cdot$ m^{-2} intravenously on day 1), and methylprednisolone (1,000 mg $\cdot$ day^{-1} intravenously on days 1 through 4 and 500 mg $\cdot$ day^{-1} intravenously on days 5 and 6). The chemotherapy was administered every 21 to 28 days. After four courses of the chemotherapy, about 65% reduction in the size of the tumor was revealed by computed tomographic scans, and his symptoms were improved.

On June 14, 1989, an operation was performed through a median sternotomy. A firm and nodular tumor was found in the anterior mediastinum, infiltrating the SVC, left brachiocephalic vein, pericardium, and the upper lobes of both lungs. Serosanguineous pericardial effusion (180 mL) was also seen. The thymus and the tumor with involved organs, which were the left brachiocephalic vein, pericardium, and both lungs, were dissected from the normal structures. Cardiopulmonary bypass was established by cannulating the right femoral artery and the inferior vena cava. After the right brachiocephalic and azygos veins were cross-clamped, the SVC was widely



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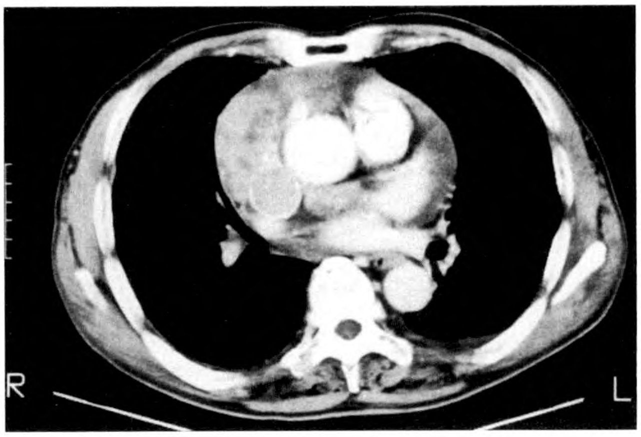

B

Fig 1. Chest computed tomographic scans showing the anterior mediastinal mass invading the superior vena cava and the pericardium, and the presence of pericardial effusion.

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opened. A large, soft, yellow mass measuring 12.0 × 2.5 × 1.8 cm was found within the SVC and the right atrium, partially adhering to the atrial wall. The tumor thrombus was removed through the right atrium, and then an en bloc resection of the tumor and the involved parts of the SVC and other neighboring structures were completed. The defect of the caval wall was repaired with a polytetrafluoroethylene graft.

Pathological examination revealed that the tumor, which measured 12.0 × 5.5 × 3.0 cm, had directly invaded the junction of the bilateral brachiocephalic veins, from where the tumor thrombus extending into the SVC and the right atrium was formed (Fig 3). Microscopically, the tumor showed the lobular configuration and was predominantly composed of round to oval epithelial cells without conspicuous cellular atypia (Fig 4). Only in a small part of it were lymphocytes seen.

Postoperatively the patient received two more courses of chemotherapy and 50.4 Gy of irradiation to the whole mediastinum. Although mild heart failure was observed for several months after the operation, he has done well clinically, and chest computed tomographic scans in March 1991 revealed no evidence of recurrence or residual tumor.

Comment

Tumor thrombosis of the vena cava or the right atrium occurs rarely and is often associated with renal cell carcinoma [1] and hepatocellular carcinoma [2]. Most of these thrombi occupy the inferior vena cava.

Invasive thymomas are characterized by an infiltrative growth and extension into the neighboring structures [3]. However, formation of a tumor thrombus in the SVC and the right atrium is a very rare mode of extension of thymoma. To our knowledge, only 3 cases of thymoma with this growth pattern have been reported in the English-language literature or abstracts [4–6]. Two of these patients had a palliative resection of the tumor by means of cardiopulmonary bypass and received postoperative radiotherapy [4, 6]. The third patient had only radiotherapy and chemotherapy [5].

In treatment of thymoma, it has been emphasized that complete resection markedly improves its outcome [7]. On the other hand, combination chemotherapy, particularly cisplatin-containing regimens, have recently been documented to be very active against invasive thymoma [8]. In our patient, although the tumor was initially unresectable, its radical extirpation was accomplished after four courses of cisplatin-containing chemotherapy, and then further chemotherapy and radiotherapy was administered. Multidisciplinary treatment, consisting of chemotherapy, operation, and radiotherapy, is thought to be very useful for advanced invasive thymoma such as in this case.

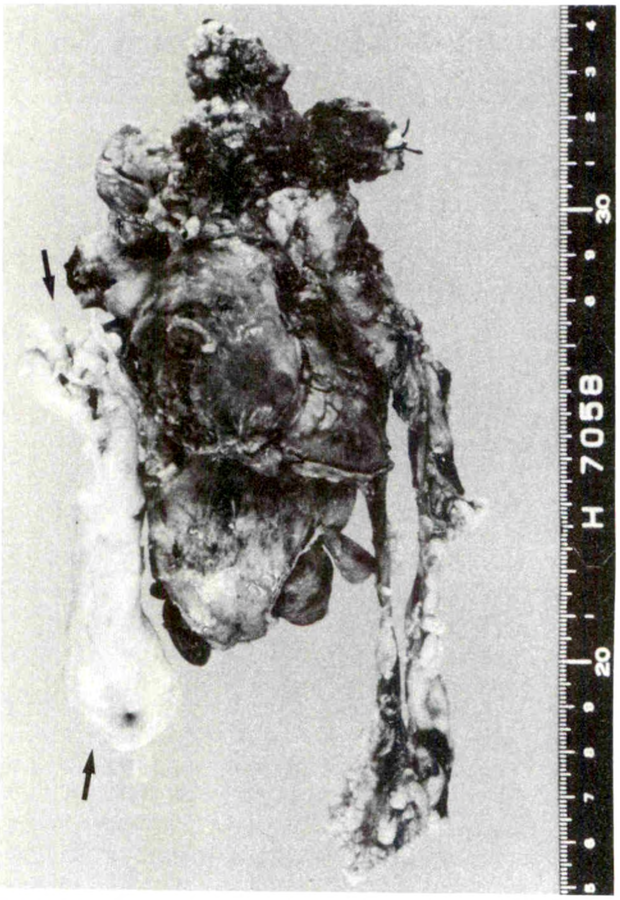

Fig 3. The resected specimen. The tumor formed a tumor thrombus extending from the junction of the bilateral brachiocephalic veins into the superior vena cava and the right atrium (arrows).

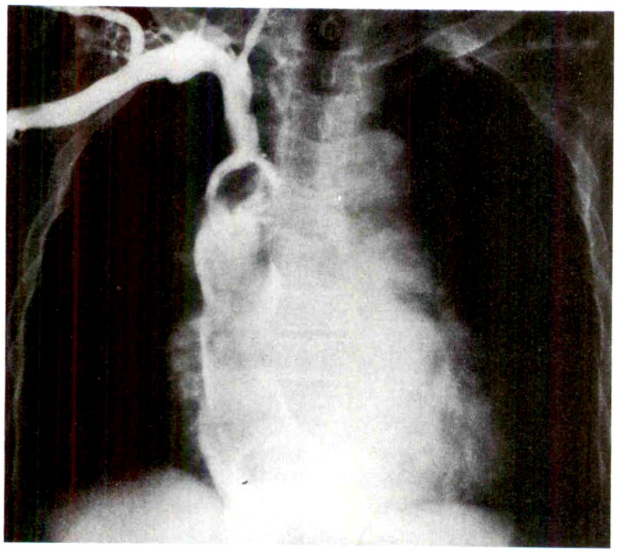

Fig 2. Superior venacavogram showing the tumor thrombus occupying the superior vena cava and the right atrium.

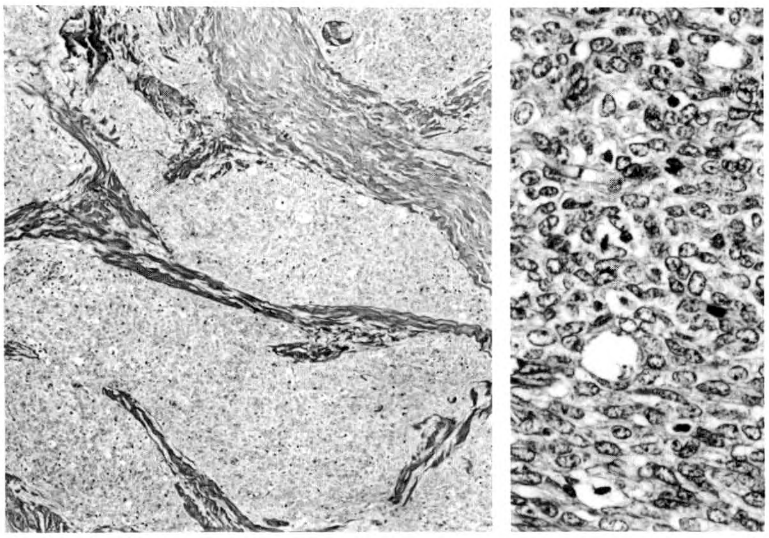

Fig 4. Microscopic appearance of the resected tumor, showing the multinodular character of thymoma (left), which is predominantly composed of round to oval epithelial cells (right). (Hematoxylin and eosin; left, ×140; right, ×350; both before 24% reduction.)

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Coronary Bypass Using Arterial Grafts in Homozygous Familial Hypercholesterolemia

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A 25-year-old man with homozygous familial hypercholesterolemia who had severe coronary artery disease underwent coronary revascularization by combined arterial grafts using bilateral internal mammary arteries and gastroepiploic artery. Early postoperative coronary angiography showed all the grafts patent without any stenosis. Because no atherosclerotic changes were seen in the specimens of each graft used, combined arterial grafting may have a role in the treatment of coronary artery disease in homozygous familial hypercholesterolemia.

(Ann Thorac Surg 1992;53:510–2)

In patients with homozygous familial hypercholesterolemia (FH), there is a greater propensity of rapid progression of severe coronary atherosclerosis, and myocardial infarction or sudden death occurs very commonly before 30 years [1]. Although coronary artery bypass grafting (CABG) has been applied in this subset of patients in the hope of preventing the ischemic events, extreme hypercholesterolemia may have a potential risk of graft closure. This may be particularly the case in the saphenous vein graft [2]. In this setting, use of arterial graft appears to be beneficial. In this report, we describe a patient with homozygous FH in whom complete coronary artery revascularization was performed using bilateral internal mammary arteries (IMAs) and right gastroepiploic artery.

A 25-year-old man known to have homozygous FH and a serum total cholesterol level reaching 18.0 mmol/L (696 mg/dL) experienced syncopal attack 3 years ago and had chest pain on exercise since then. His mother was known to have homozygous FH and died of myocardial infarction at the age of 40 years. His father was also found to have heterozygous FH. This homozygous FH was also detected in his two uncles on the maternal side, and both underwent CABG at the age of 24 and 28 years, respectively [3].

Physical examination showed numerous xanthomas over the knees, ankles, elbows, hip, and interdigital spaces. The Achilles tendon was thickened to 40 mm. The diagnosis of homozygous FH was confirmed by the assay of low-density lipoprotein receptor using skin fibroblasts with the receptor activity of approximately 1% of normal controls. He was designated as a homozygote of receptor-negative type. Cardiac examination revealed a grade 3/6 diastolic murmur maximal at the fourth left intercostal space. A resting electrocardiogram revealed T wave inversion over the inferior and anterior leads. Echocardiography showed thickening of the aortic valve and calcification of the aortic root. Color Doppler examination showed moderate degree of aortic regurgitation. Thallium 201 myocardial scintigraphy demonstrated myocardial ischemia in the anterior and the inferior lesions. Selective coronary angiography showed complete occlusion of the left anterior descending coronary artery and the right coronary artery with good collaterals from the circumflex coronary artery to them. Left ventriculography showed global hypokinesis in wall motions with an ejection fraction of 0.51.

Coronary revascularization was indicated, and this was performed using arterial grafts in situ exclusively: the right IMA was grafted to the right coronary artery, the left IMA to the diagonal branch, and the right gastroepiploic artery to the left anterior descending artery. Postoperative coronary angiography performed 2 months after CABG revealed all the grafts patent without any stenosis (Fig 1). Left ventriculography showed improved left ventricular wall motion with an ejection fraction of 0.73. There was no arteriosclerotic change seen at histological examination of each graft stump harvested at the operation (Fig 2). In addition to lipid-lowering agents, low-density lipoprotein apheresis was continued every 2 weeks, maintaining serum cholesterol level around 5.2 mmol/L (200 mg/dL).

Comment

Homozygous FH is an autosomally dominant inherited disorder associated with accelerated atherosclerosis, especially premature coronary artery disease. Although the incidence of homozygous FH is very small, estimated to be one per million in the general population [1], some patients with this disorder have been reported to undergo coronary revascularization [3–6]. In recent years, IMA has become the choice for CABG because of the enhanced long-term patency it provides. Atherosclerosis is likely to

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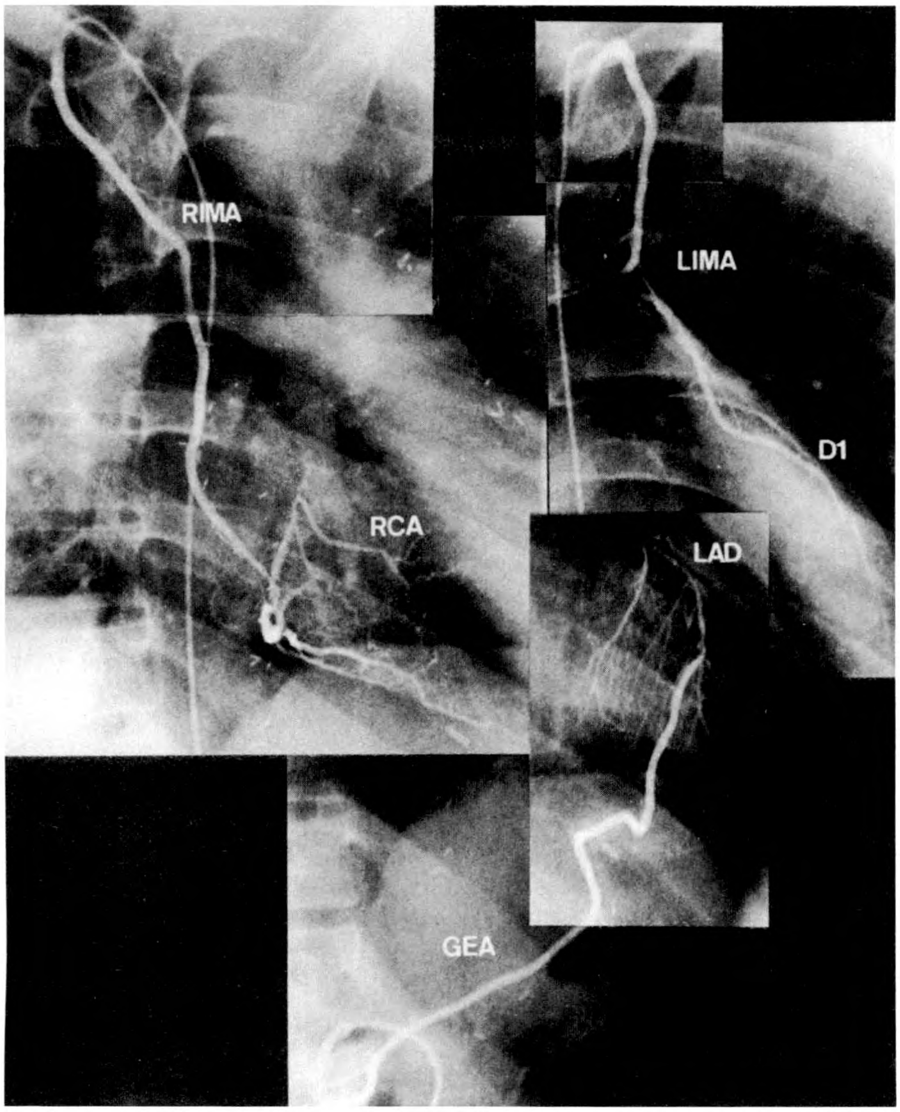

Fig 1. Postoperative coronary angiogram (D1 = diagonal branch; GEA = gastroepiploic artery; LAD = left anterior descending artery; LIMA and RIMA = left and right internal mammary artery; RCA = right coronary artery.)

occur in the majority of vein grafts within 10 years after operation, but this is hardly seen in IMA grafts so far [7]. Because hypercholesterolemia may accelerate atherosclerotic change of vein grafts, the IMA graft appears more advantageous, especially in FH. On the other hand, gastroepiploic artery has recently been recognized as a suitable conduit for CABG because of its lower rate of atherosclerotic change [8]. For this reason, we performed CABG using GEA in addition to IMA in situ in this patient with homozygous FH.

Although use of arterial grafts appears to be advantageous in this setting, the degree of atherosclerotic change of these arterial conduits in homozygous FH have not been clarified. In our case, no sclerotic change was recognized by the histological examination of arterial conduits. Therefore, these arterial conduits can be expected to be advantageous for CABG in homozygous FH. However, long-term analysis is required for this issue.

From the technical aspect of CABG, conventional saphenous vein bypass grafting increases the risk of dislodging and embolizing atherosclerotic plaques from the ascending aorta at the time of operation because of the placing of side clamps for proximal anastomosis. Atherosclerotic change of the ascending aorta is usually seen in these patients. Therefore, saphenous vein grafts should be avoided as much as possible in such a case to prevent embolization of atheromatous plaques. On the other hand, stenosis of the branches of the aortic arch and abdominal aorta has been reported in FH [1]. Internal mammary artery or gastroepiploic artery may not be suitable if there is stenosis at these vessels at the junction from the ascending aorta, the subclavian artery, or the celiac artery. Thoracic aortograms and selective angiography of these arteries may be necessary before using these arterial conduits in homozygous FH.

Perhaps because of the rare occurrence of homozygous FH and the short life expectancy, this case report is unusual in that we report CABG in a homozygous son of a homozygous mother. His mother suddenly died of heart attack. Although his uncles are alive long after CABG

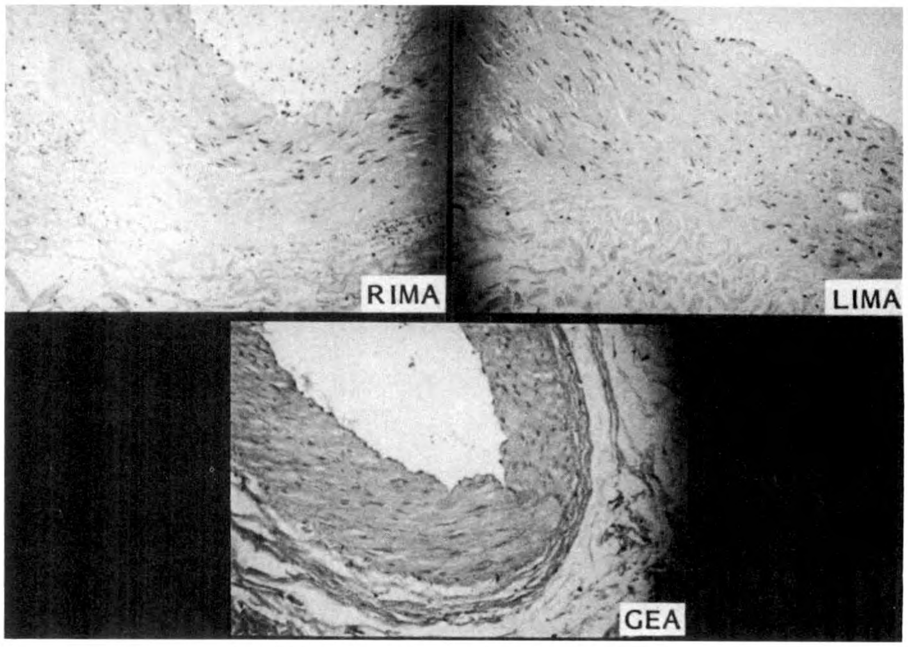

Fig 2. Histology of the right internal mammary artery (RIMA), left internal mammary artery (LIMA), and gastroepiploic artery (GEA).

with saphenous vein grafts, one of them has angina pectoris because of occlusion of the saphenous vein grafts [3]. Combined arterial grafts and periodic low-density lipoprotein apheresis to maintain a reduction in the low-density lipoprotein cholesterol level may offer promise for coronary artery disease in homozygous FH.

We thank Tokio Yamaguchi, MD, for his histological review.

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Internal Thoracic Artery Grafting for Congenital Coronary Malformations

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We report 2 patients with congenital coronary anomalies (atresia of left main coronary artery and anomalous origin of the left coronary artery from the pulmonary artery) successfully treated with single or double internal thoracic artery grafting. Because the internal thoracic artery has a potential for circumferential as well as longitudinal development, and because of the uncertainty of ultimate vein graft function, we believe that the internal thoracic artery is the best graft material for the treatment of congenital coronary malformations requiring bypass operation in children, adolescents, or even in adults.

(Ann Thorac Surg 1992;53:513–6)

Coronary artery bypass grafting has been occasionally performed for some congenital malformations of the coronary arteries such as atresia of the left main coronary trunk, anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), and anomalous left coronary artery originating from the right sinus of Valsalva or anomalous right coronary artery arising from the left aortic sinus of Valsalva [1–7]. In the early era of coronary bypass grafting for congenital coronary artery anomalies, the saphenous vein graft was used [1]. The subclavian artery was then used as a conduit for the treatment of ALCAPA [2, 3]. In recent years, however, the internal thoracic artery (ITA) graft has become more popular for this purpose [4, 5] because of the long-term patency and function of the ITA graft and also because of the uncertainty of late vein graft function. Because there has been a very limited number of reports regarding the use of ITA grafts for the treatment of congenital malformations of the coronary arteries, we herein describe 2 patients treated with single and double ITA grafts for left main trunk atresia and ALCAPA.

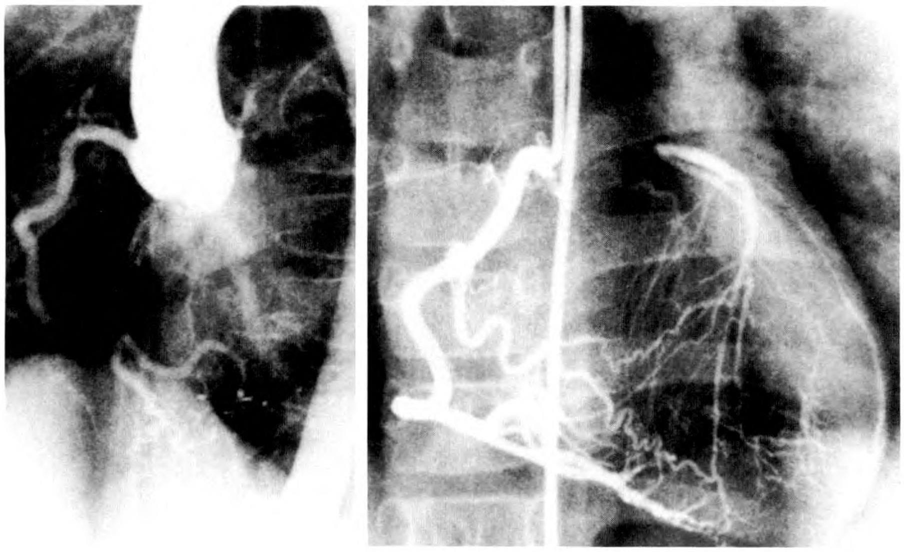

Fig 1. Preoperative aortic and coronary angiograms of patient 1. There was no demonstrable left coronary orifice in the aorta, and the left coronary artery was retrogradely perfused from the somewhat enlarged right coronary artery.

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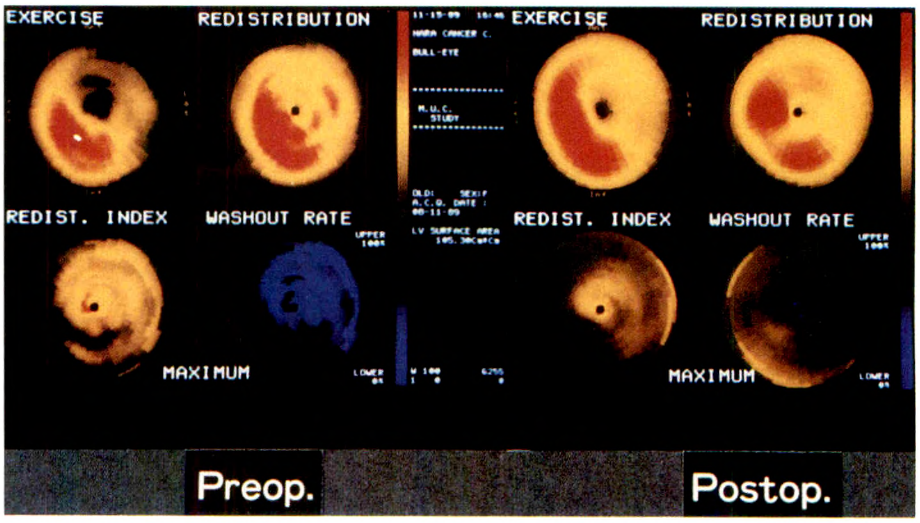

Fig 2. (Patient 1.) Preoperative and postoperative thallium 201 myocardial scintigrams during exercise. Apparent anterolateral ischemia with late redistribution during exercise improved remarkably after the operation.

Case Reports

Patient 1

A 7-year-old girl, 124 cm tall and weighing 24 kg, was evaluated for a grade 4/6 loud pansystolic murmur, moderate cardiomegaly, and electrocardiographic signs of left ventricular hypertrophy ($RV_5 = 3.3$ mV) and small Q waves in leads III and aVF. Exercise electrocardiogram at the heart rate of 126 beats/min showed a substantial ST-T depression of 2 to 3 mm in leads V_4 to V_6. Cardiac catheterization and angiocardiography demonstrated the presence of severe (grade 4/4) mitral regurgitation and atresia of the left main trunk, filled retrogradely from the right coronary artery as shown in Figure 1. The intracardiac pressures were normal at rest in spite of the presence of severe mitral regurgitation, and the global left ventricular contraction was preserved with an ejection fraction of 0.62, although mild anterolateral hypokinesis was observed on cineangiograms. Thallium 201 myocardial scintigraphy during exercise demonstrated the apparent presence of ischemia with late redistribution at the anterolateral area of the left ventricle (Fig 2).

At operation, the left ITA (1 mm in diameter) was dissected free first and then, under cardiopulmonary bypass, the left atrium was opened. The mitral valve was pliable and the anterior leaflet was prolapsed. The annulus was also dilated, with a 25-mm probe easily passing

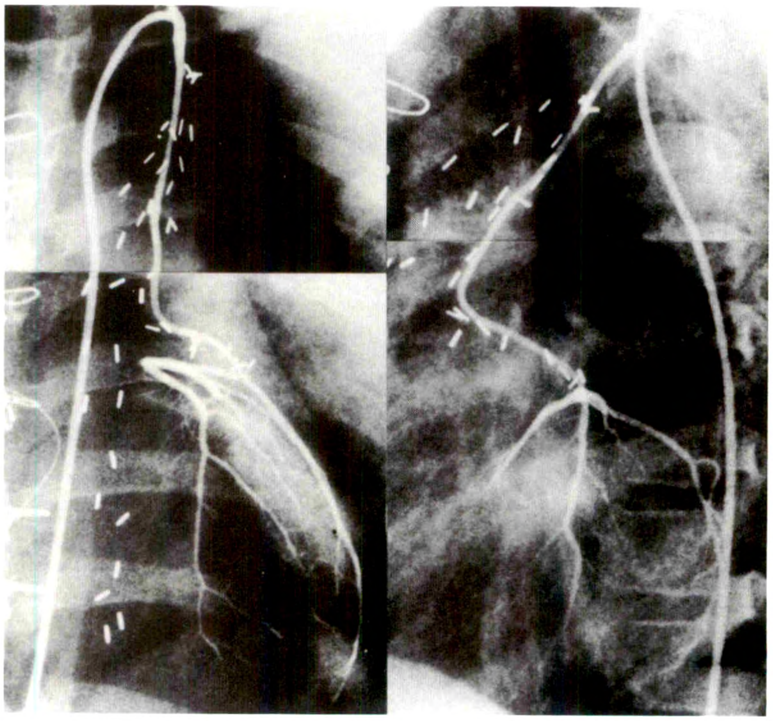

Fig 3. (Patient 1.) Postoperative left internal thoracic arteriography revealed good perfusion to the left coronary artery system.

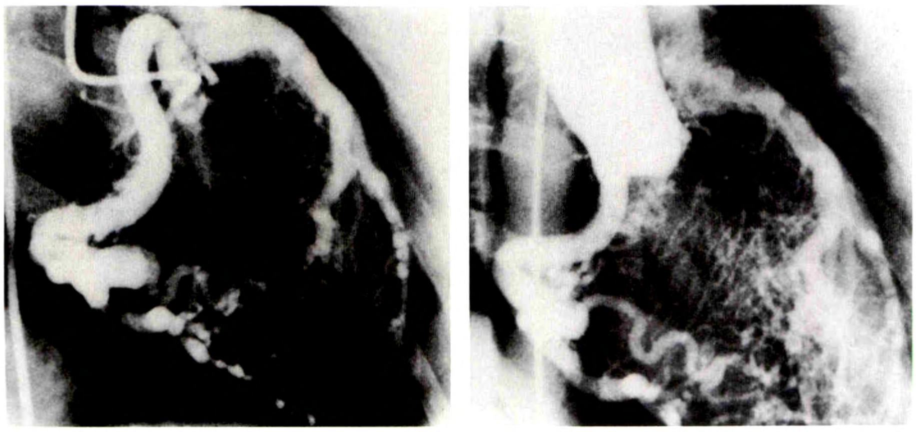

Fig 4. (Patient 2.) Preoperative right coronary arteriography demonstrated an enlarged right coronary artery with an extensive collateral network to the left coronary artery, eventually draining into the pulmonary artery.

through. Anterolateral and posteromedial annuloplasty with 3-0 Gore-Tex (W.L. Gore & Assoc, Flagstaff, AZ) sutures was performed in addition to chordal shortening of the anterior leaflet connected to the posteromedial papillary muscle. The mitral annuloplastic procedure was guided by transesophageal echocardiography. The left ITA was then anastomosed to the bifurcation area between the anterior descending artery and the first diagonal branch because the entire left anterior descending artery was embedded intramuscularly. Cardiopulmonary bypass was terminated without a problem, and transesophageal echocardiography confirmed the substantial improvement in mitral regurgitation, though it had not completely disappeared.

Postoperative studies revealed patency of the left ITA graft (Fig 3), resulting in substantial improvement of ischemia at the anterolateral aspect of the left ventricle (see Fig 2). The mitral regurgitation was substantially reduced as well (grade 1 to 2/4).

Patient 2

A 45-year-old woman was referred to us because of effort angina pectoris with ST-T depression in leads V_4 to V_6. The electrocardiogram at rest showed a normal sinus rhythm and a sign of left ventricular hypertrophy ($SV_1 + RV_5 = 5.1$ mV). Coronary arteriography confirmed the diagnosis of ALCAPA with a left to right shunt ratio of 1.31 (Fig 4). Preoperative exercise thallium 201 myocardial scintigraphy revealed anteroseptal and inferolateral ischemia with late redistribution as shown in Figure 5. The left ventricular end-diastolic pressure was borderline elevated to 12 mm Hg.

Operation was scheduled at first to perform reimplantation of the left coronary ostium to the aorta, but the plan was changed because the left coronary artery was anomalously originating from the left posterior pulmonary sinus and because of excessive hemorrhage present during the dissection of the left coronary artery to obtain the needed length to reach the aorta due to extensive collateral networks. The procedure performed, therefore, was ligation of the coronary artery at the pulmonary artery and bilateral ITA bypass grafting to the left anterior descending artery and the circumflex artery.

The postoperative recovery was uneventful. Angiography performed 1 month after operation clearly demonstrated patency of the bilateral ITA grafts (Fig 6), although the left anterior descending artery was still large and bidirectionally perfused from both the right ITA and the

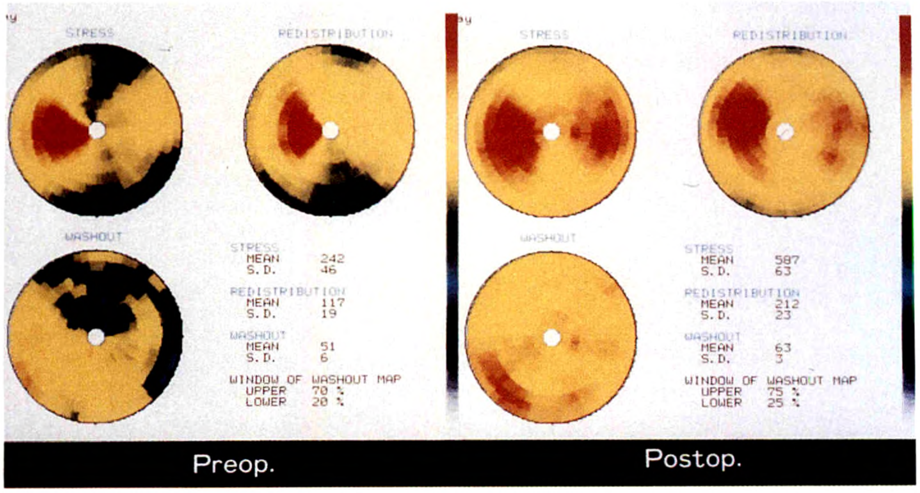

Fig 5. (Patient 2.) Preoperative and postoperative exercise thallium 201 myocardial scintigrams. Preoperative ischemia with late redistribution at the anteroseptal and inferolateral regions improved remarkably after the operation.

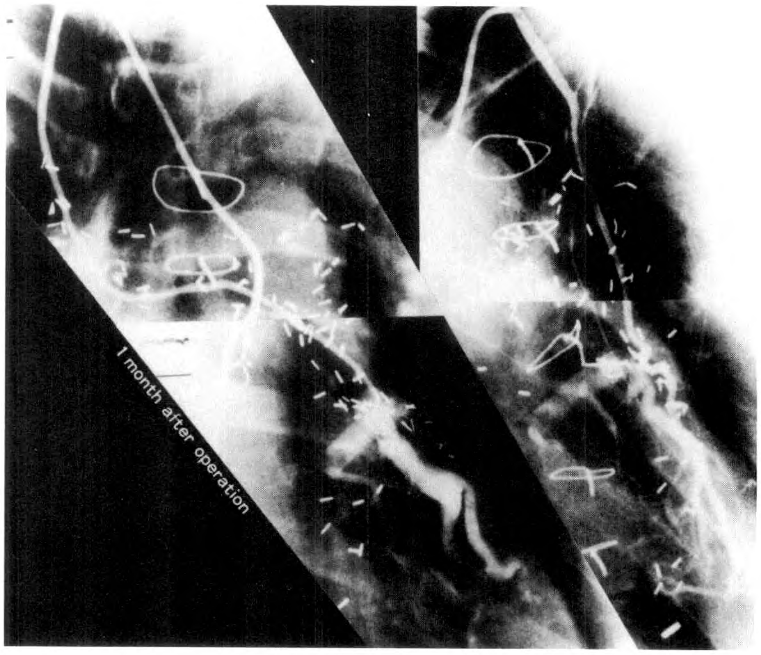

Fig 6. (Patient 2.) Both the right internal thoracic artery graft to the left anterior descending artery and the left internal thoracic artery graft to the circumflex artery were patent 1 month after the operation. The left anterior descending artery, however, was still very large and perfused bidirectionally through the graft and large collateral vessels from the right coronary artery.

large collateral vessel from the right coronary artery. Thallium 201 myocardial imaging showed remarkable improvement in perfusion of the left ventricle (see Fig 5).

Comment

Myocardial revascularization procedures have been performed to treat congenital coronary artery abnormalities for many years [1–7]. The saphenous vein graft mainly used from the earlier period of operation has a high attrition rate even though it is used for nonatherosclerotic disease [1, 8]. Therefore, recent reports [4, 5] deal with the use of ITA for the treatment of coronary malformations. For ALCAPA, the coronary transfer method is the most physiologic operative procedure and may be the treatment of choice for children, but this method is more difficult to apply in adult patients than in children because of the requirement of longer dissection of the anomalous left coronary artery surrounded by extensive collateral networks. Similar experience has been noted by Moodie and associates [6]. Coronary artery bypass operation with the use of ITA combined with ligation of the anomalous connection is suggested as an alternative method, particularly in adults [7], but no such report has yet appeared. We consider use of bilateral ITAs to be desirable to revascularize the left coronary system because the ITA is much smaller than the enlarged coronary artery in this anomaly. For this reason, we performed bilateral ITA grafting for the treatment of ALCAPA in adults with a successful result.

Because the ITA has a potential for circumferential as well as longitudinal development according to coronary flow requirements and patient growth [8], we believe that the ITA is the best graft material for the treatment of congenital coronary artery abnormalities requiring bypass operation in children, adolescents, or even in adults.

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Paraganglioma of the Posterior Mediastinum: Value of Magnetic Resonance Imaging

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A case of paraganglioma arising in the posterior mediastinum in a 29-year-old man diagnosed by magnetic resonance imaging is reported. Excision of mediastinal paraganglioma is often hazardous because of its rich vascular supply and tendency to involve surrounding structures. Magnetic resonance imaging is valuable for the preoperative diagnosis of this vascular tumor as well as for determination of its resectability and appropriate surgical procedure.

(Ann Thorac Surg 1992;53:517–9)

Paraganglioma of the posterior mediastinum is a rare neurogenic tumor arising from the aorticosympathetic paraganglia [1]. Because of the vascular nature of the tumor, angiography has been reported to be important for its diagnosis [2, 3]. We wish to present a case in which magnetic resonance imaging (MRI) was used to determine both the vascular nature and the extent and relation of the tumor to surrounding structures.

In July 1990, a 29-year-old man without symptoms was admitted to our hospital for evaluation of an abnormal density on a chest roentgenogram. On admission, blood pressure was 130/80 mm Hg and pulse rate was 70 beats per minute and regular. Results of other physical examination were normal. Laboratory studies including measurement of levels of urinary catecholamines, urinary vanillylmandelic acid, and urinary metanephrines showed normal results.

Chest roentgenogram (Fig 1) and computed tomogram revealed a left posterior mediastinal mass at the level of the fifth, sixth, and seventh paravertebral sulci. Whole-body computed tomography revealed no other tumors.

Magnetic resonance examination of the chest was performed. Axial T1-weighted images revealed a tumor with nonhomogeneous intermediate signal intensity with multiple signal-free areas suggesting signal void (Fig 2A); whereas, on axial T2-weighted images, it had high signal intensity (Fig 2B). The borders of the tumor were well defined. Magnetic resonance images showed no evidence of tumor invasion of adjacent structures (descending aorta, chest wall, and thoracic vertebrae) and no extension of intrathoracic tumor into the intraspinal space through intervertebral foramina (Figs 2A–C).

Left thoracotomy was performed on August 21, 1990; arterial pressure and electrocardiogram were monitored continuously. A soft, circumscribed, extrapleural mass was present in the costovertebral sulcus. The tumor was extremely vascular and firmly adherent to the adjacent vertebral column and fifth, sixth, and seventh ribs, but it did not invade these structures. During dissection, profuse hemorrhage occurred. The tumor was excised en bloc with an estimated blood loss of 1,500 mL. No remarkable changes in blood pressure or heart rate occurred during the operation.

The excised tumor measured 6.5 × 5.0 × 3.0 cm and weighed 50 g. The cut surface was a reddish-tan color with areas of hemorrhage, and high vascularity was noted. Microscopic sections revealed that this tumor was composed of large cells with abundant eosinophilic granular cytoplasm and ovoid vesicular nuclei arranged in an alveolar pattern with a highly vascular intervening

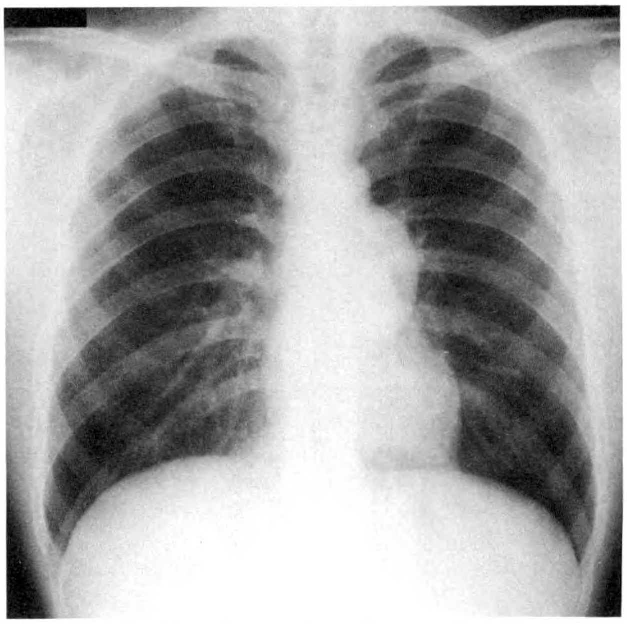

Fig 1. Chest roentgenogram shows a left posterior mediastinal mass.

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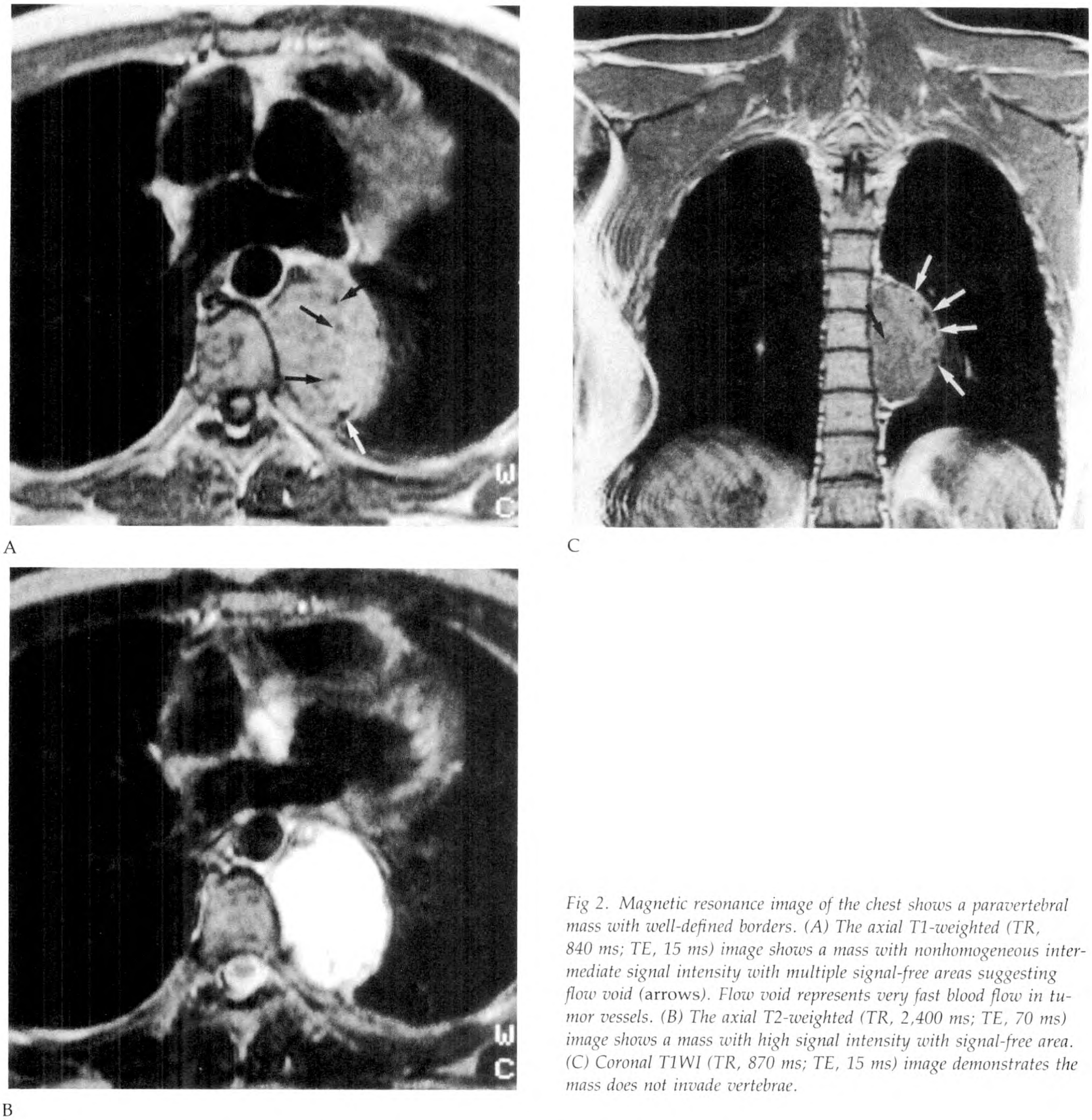

Fig 2. Magnetic resonance image of the chest shows a paravertebral mass with well-defined borders. (A) The axial T1-weighted (TR, 840 ms; TE, 15 ms) image shows a mass with nonhomogeneous intermediate signal intensity with multiple signal-free areas suggesting flow void (arrows)*. Flow void represents very fast blood flow in tumor vessels. (B) The axial T2-weighted (TR, 2,400 ms; TE, 70 ms) image shows a mass with high signal intensity with signal-free area. (C) Coronal T1WI (TR, 870 ms; TE, 15 ms) image demonstrates the mass does not invade vertebrae.*

stroma. Grimelius staining demonstrated chromaffin-positive granules in the cytoplasm of tumor cells. The final diagnosis was paraganglioma of the posterior mediastinum.

Comment

Glenner and Grimley [1] have classified the extraadrenal paraganglia into four groups on the basis of anatomic distribution, innervation, and microscopic structures: (1) branchiometric; (2) intravagal; (3) aorticosympathetic; and (4) visceral-autonomic. Mediastinal paragangliomas occur most frequently in the middle compartment in association with the branchiometric paraganglia, and much less frequently in the posterior compartment in association with the aorticosympathetic paraganglia; only 40 cases of paraganglioma arising in the posterior mediastinum have been reported in the English-language literature.

Excision of a posterior mediastinal paraganglioma is often difficult and hazardous because of the rich vascular supply and the tendency of the tumor to involve surrounding structures [2–5]. Small [4] reported a case of dumbbell-shapped paraganglioma in which intrathoracic tumor extended into the intraspinal space through the intervertebral foramen. Both laminectomy and thoracotomy were required in that case to achieve complete excision; however, profuse bleeding made it impossible to excise all of the tumor. Preoperative angiography to assess the vascularity and computed tomography to evaluate the extent of tumor have been reported to be valuable [2, 3]. Magnetic resonance imaging is superior to computed tomography for evaluation of mediastinal tumors because the coronal and sagittal as well as axial magnetic resonance images enable determination of the overall tumor extent and the good contrast of soft tissues and vessels obtained with MRI enables easy distinction between tumor and great vessels [6]. In addition, MRI may noninvasively and safely provide information about the vascularity of tumor as flow void, which represents very fast blood flow in its vessels, whereas angiography in case of paraganglioma is often hazardous because intraatrial injection of contrast medium may cause a severe cardiovascular crisis [3].

In this case, we used MRI to diagnose posterior mediastinal paraganglioma. The tumor was delineated as a nonhomogeneous mass with intermediate signal intensity on axial T1-weighted images and high signal intensity on axial T2-weighted images, as seen in other mediastinal tumors [6], and with flow void. Mediastinal tumors with high vascularity are limited to only four entities: Castleman's disease, hemangioma, goiter, and paraganglioma [2]. Hemangioma consists of a lake of slowly flowing blood, and does not produce intravascular signal void on MRI. Paraganglioma is one of the diagnoses of an intrathoracic paravertebral mass with flow void on MRI.

In cases of intrathoracic paravertebral tumor, MRI should be performed not only to determine the extent of tumor but also to investigate the possibility of paraganglioma, because functional paraganglioma may produce cardiovascular complications during operation without preoperative α- and β-blockade therapy. Even when the patient shows no symptoms of excessive catecholamine secretion before operation, manipulation of the tumor may induce hypertensive crisis, tachycardia, and cardiac arrhythmia [4].

Recently, iodine 131-metaiodobenzylguanidine has been proved to be very useful for localization of paraganglioma [7]. Because we were unable to use this new radiopharmaceutical technique, whole-body computed tomography was employed to detect possible multiple paragangliomas.

In conclusion, MRI is most useful for diagnosing and evaluating the extent of paraganglioma of the posterior mediastinum, and in planning the complete excision of the tumor.

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Total Anomalous Pulmonary Venous Connection: Surgical Correction in a 66-Year-Old Man

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A cyanotic, debilitated 66-year-old man was referred as an emergency because of embolic arterial occlusion of the left lower extremity. Subsequent investigation revealed total anomalous pulmonary venous connection. Complete surgical correction was accomplished. Despite a difficult postoperative hospital course, more than 3 years after operation he continues to experience improved quality of life with better exercise tolerance, freedom from further emboli and symptomatic arrhythmias, and no need for his previously routine phlebotomies.

(Ann Thorac Surg 1992;53:520–2)

Although representing only a small fraction of those patients with total anomalous pulmonary venous connection, rare individuals survive into adulthood without diagnosis [1–3]. The oldest survivor heretofore reported, in whom death occurred at age 62 years, was diagnosed at autopsy [4]. The risk of surgical correction is quite low in children and young adults [5]. However, when diagnosis is made in an elderly, debilitated individual, assessment of operative risk becomes difficult, clear precedent for correction is meager, and the decision to proceed may be a difficult one.

A 66-year-old man was referred to us in October 1988 after sudden onset of severe pain and pallor in his left leg below the knee. Examination revealed a frail individual with marked cyanosis and clubbing of the digits. The left lower extremity was pale, cool, and without popliteal or pedal pulses.

Past history was significant for cyanosis since birth and for frequent respiratory infections and retarded physical development during childhood. In the fifth decade regular phlebotomies for polycythemia began. Anticoagulation with warfarin had been instituted elsewhere for transient cerebral ischemic events but was discontinued because of nosebleeds. Dipyridamole was administered but produced nausea. Nine days before admission a transient ischemic neurologic event accompanied by a grand mal seizure occurred. Episodes of supraventricular tachycardia were occurring with increasing frequency. Referral for specific cardiac diagnosis had not been sought because the patient believed that his age and debilitated condition precluded aggressive intervention.

The evening of admission, embolectomy with a Fogarty catheter restored circulation to the left lower extremity. Heparin followed by warfarin anticoagulation was begun. Computed tomographic scanning of the head revealed two areas of prior infarction. Transthoracic echocardiography with color flow Doppler examination showed normal left ventricular size and function with paradoxical ventricular septal motion, enlargement of the right atrium and ventricle, a large secundum atrial septal defect with bidirectional shunting, and a dilated coronary sinus that received the pulmonary veins. Arterial oxygen tension on room air was 46 mm Hg. At catheterization, pulmonary artery pressure was 29/18 mm Hg and pulmonary vascular resistance was 160 dynes $\cdot$ s $\cdot$ cm^{-5}. Flows [6] were as follows: pulmonary, 7.0 L/min; systemic, 4.7 L/min; and effective, 2.4 L/min.

On the eleventh hospital day, repair was performed through a median sternotomy. After institution of cold blood cardioplegia, the right atrium was opened. The common tissue separating the coronary sinus and the left atrium was incised, and the margins were closed with a continuous suture. In the manner described by Reardon and associates [7], a Dacron baffle was inserted so as to close the atrial septal defect and to direct coronary sinus blood flow, and consequently pulmonary venous return, into the left atrium.

Initially, mental obtundation complicated postoperative management. Copious pulmonary secretions and associated coughing led to sternal dehiscence necessitating reclosure and to two periods of reintubation. Anticoagulation with warfarin, begun because paroxysms of atrial flutter raised fears of further systemic emboli, was followed by an episode of massive gastrointestinal bleeding. Warfarin administration was discontinued. By the 30th postoperative day, he had recovered adequately to be discharged, his only medications being digoxin (0.125 mg daily) and propranolol (10 mg twice daily) for control of supraventricular arrhythmias and aspirin (80 mg daily). Over follow-up of 38 months, he has resumed his former activities, has experienced no recurrent embolic events, has a normal hematocrit without further phlebotomies, and reports that his exercise tolerance has greatly improved compared with the period preceding surgical repair. He has had no symptomatic arrhythmias and has remained in sinus rhythm on subsequent electrocardiograms.

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Comment

Although sometimes accompanied by other malformations, total anomalous pulmonary venous connection usually occurs, as it did in this patient, as an isolated lesion [3]. The majority of patients with total anomalous pulmonary venous connection die in infancy. However, several features seem to enhance the chances for prolonged survival: a short and unobstructed route of anomalous connection, a large interatrial communication, normal pulmonary vascular resistance, and the absence of major systemic oxygen desaturation [2, 3, 5]. This patient fared well in these regards except for the severity of hypoxemia and consequent cyanosis.

Surgical correction is unquestionably the treatment of choice for the previously undiagnosed child or young adult in otherwise good health. However, in older individuals there is little direct precedence for repair as the oldest such patient heretofore reported was 55 years old [7]; few patients beyond the age of 30 years have been described. Follow-up showing improved survival or quality of life has not been presented. Interestingly, in a review published well into the era of repair with the use of cardiopulmonary bypass, operation "was not advised" for an active and apparently otherwise healthy 46-year-old patient with total anomalous pulmonary venous connection despite symptoms similar to those of our patient [2]. The closest analogy to which one might appeal is probably correction of atrial septal defect, in which the results of repair in older patients have been better investigated [8, 9].

Responding appropriately to this man's multiple systemic emboli was problematic. Two sources seemed most likely: the left atrium as a result of paroxysmal supraventricular arrhythmias and the systemic veins through paradoxical embolization. Chronic anticoagulation with warfarin was proscribed by his history. Closure of the atrial septal defect, antiplatelet therapy with low-dose aspirin, and amelioration of the atrial arrhythmias have eliminated embolic events thus far. Fortunately, there has been no recurrent gastrointestinal bleeding despite aspirin therapy.

In conclusion, undiagnosed cyanotic congenital heart disease in older patients is unusual in this country. Even when surgical correction appears technically feasible, the decision to proceed may be a complex one for the patient, the patient's family, and the involved physicians. Risk is increased [9] and postoperative care may be difficult. However, if initial obstacles can be surmounted, relief of symptoms and marked and sustained improvement in life quality may be expected.

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INVITED COMMENTARY

The report by McMullan and Fyke shows again that congenital cardiac anomalies can be successfully corrected in adult patients. Although some cardiologists contend that the operative risk does not justify the expected benefit, the decision to repair cardiac anomalies should depend on the physiology of the defect and the extent of the disability, rather than the patient's age. In a 66-year-old patient with low pulmonary vascular resistance, the risk should be no greater than that of repairing a large secundum defect. My colleagues and I have successfully corrected total anomalous pulmonary venous return in 4 patients with cyanosis who were more than 30 years of age (32, 49, 53, and 55 years). In our patients who underwent repair of tetralogy of Fallot, 29 were older than 30 years; the oldest was 73!

Survival of patients born with total anomalous pulmonary venous return depends on several factors. In newborns, obstruction of the venous return is life-threatening, with infracardiac and infradiaphragmatic connections producing the highest mortality rates. The length of the venous connection is also important. In the report by McMullan and Fyke, the patient's defect was of the paracardiac type, which has the shortest possible connection. This short connection probably accounted for the patient's survival into his seventh decade. Another factor critical to patient survival in total anomalous pulmonary venous return is the diameter of the atrial defect. In newborns, balloon septoplasty has been used as palliation and preparation for subsequent repair. In patients between 2 and 12 years of age, the surgical repair of total anomalous pulmonary venous return carries a risk similar to that of simple repair of atrial septal defect.

The source of systemic emboli in the patient reported by McMullan and Fyke is conjectural. I disagree with their conclusion that the emboli originated in the left atrium. I suspect, instead, that the emboli originated in the systemic venous system and passed through the patent atrial septum.

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Notice From the Southern Thoracic Surgical Association

The Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel (near Tampa), Florida, November 5–7, 1992. The Postgraduate Course will be held the morning of Thursday, November 5, 1992, and will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1992, to Walter H. Merrill, MD, Program Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic Surgery*. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1992 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1992, and forwarded to John P. Clarke, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

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Diverticuloplasty for Severe Mucosal Injury After Cricopharyngeal Myotomy

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Cricopharyngeal myotomy with either diverticulopexy or diverticulectomy is the recommended therapy for Zenker's diverticulum. Mucosal injury during myotomy is rare and usually can be managed by direct mucosal closure. A technique is described to repair a serious mucosal defect that may occur during cricopharyngeal myotomy.

(Ann Thorac Surg 1992;53:523–4)

A 70-year-old woman had a 4-year history of progressive cervical dysphagia with worsening of symptoms over the recent 3 months. This was complicated by frequent regurgitation of undigested food, nocturnal aspiration and coughing, and intermittent hoarseness. A barium swallow revealed a moderate-sized Zenker's diverticulum, the body of the esophagus was normal, and there was no demonstrable gastroesophageal reflux. Esophageal motility testing showed strong pharyngeal contractions, incoordinate relaxation of the cricopharyngeus, and normal peristalsis in the body of the esophagus. Flexible esophageal endoscopy was attempted under local anesthesia but was unsuccessful. A submucosal hematoma developed on the posterior pharyngeal wall. One week later, both rigid and flexible esophagoscopy were again tried under general anesthesia immediately before myotomy; however, the esophagus could not be intubated.

Exposure of the cervical esophagus was through a standard left neck incision. After dissection of the Zenker's diverticulum, a 36 Maloney bougie was passed and a myotomy performed. The cricopharyngeus was not hypertrophic, and the plane between the circular esophageal muscle and submucosa was edematous and hemorrhagic. While the myotomy was performed, several small holes were made in the esophageal mucosa. Rather than repair each perforation, the surgeon continued the myotomy through the esophageal mucosa to the neck of the diverticulum. The inferior wall of the diverticulum was excised, and the superior wall was used to patch the esophageal defect with interrupted 4-0 Vicryl sutures (Fig 1). There was no leak demonstrated by barium swallow performed 4 days postoperatively, so oral feeding was resumed and the patient was discharged 2 days later.

Comment

The surgical management of Zenker's diverticula has evolved over the years as improvements in esophageal manometry defined the pathophysiology of the upper esophageal sphincter. Cricopharyngeal myotomy is an integral part of surgical correction of this disorder. Myotomy alone achieves improvement in symptoms in 78% of patients [1]. Most authors, however, recommend either suspension of the diverticulum (diverticulopexy) or amputation of the diverticulum (diverticulectomy) in addition to surgical myotomy [2–4].

Routine endoscopy of all patients before myotomy is not necessary. Despite the frequent association of hiatal hernia in patients with Zenker's diverticula, symptomatic gastroesophageal reflux or its complications are rare [5]. Patients with serious gastroesophageal reflux symptoms should have 24-hour pH studies to assess the severity of reflex before myotomy. Endoscopic assessment of the distal esophagus is absolutely indicated before myotomy only if pathology in the distal esophagus is suggested on barium swallow. Endoscopy is safe if the endoscope passes the cricopharyngeus effortlessly. Otherwise, endoscopy should be deferred until after cricopharyngeal myotomy, because vigorous attempts to pass an endoscope beyond a spastic cricopharyngeal muscle risk mucosal injury. In this case, endoscopic trauma produced a submucosal hematoma that predisposed the mucosa to injury during the myotomy.

Injury to esophageal mucosa while performing cricopharyngeal myotomy is infrequent. When a small mucosal injury is identified intraoperatively, primary mucosal closure and cervical drainage usually suffices. Major mucosal disruption cannot be repaired primarily because a difficult stricture will result. Liston and Manlove [6] used a Zenker's diverticulum flap to repair a pharyngeal defect after excision of a posterior pharyngeal wall carcinoma. The mucosa and submucosa in a chronic diverticulum is hypertrophic with a rich blood supply, and is an excellent flap for pharyngeal or proximal esophageal reconstruction. We do not advocate diverticuloplasty routinely for patients with a Zenker's diverticulum because myotomy combined with either diverticulopexy or diverticulectomy achieves excellent results in most patients [1, 2, 5]. If a severe mucosal tear occurs during myotomy and primary

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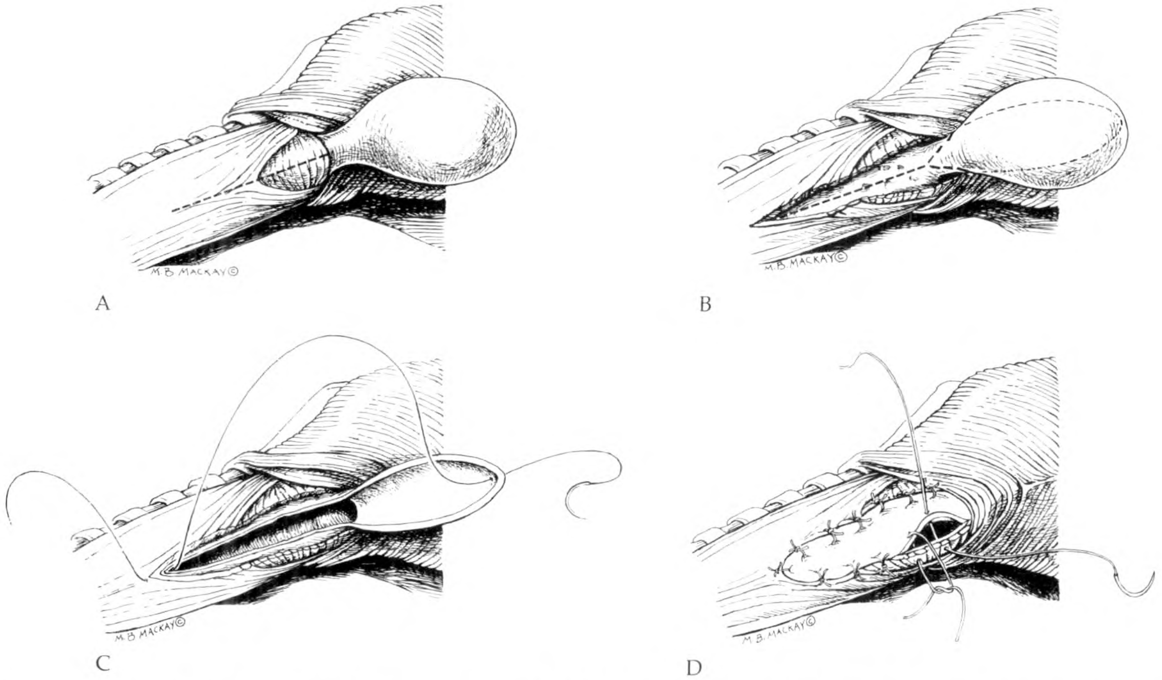

Fig 1. The technique of cricopharyngeal diverticuloplasty. (A) Myotomy is initiated from the neck of the diverticulum and continues through the cricopharyngeus and onto the body of the esophagus. (B) After completion of the myotomy, the esophageal mucosa is opened and the inferior half of the diverticulum is excised. (C) The superior portion of the diverticulum is anastomosed to the esophageal defect with full-thickness interrupted absorbable sutures. (D) Near completion of the repair: The diverticular mucosa has patched the full-thickness defect in the esophagus, preventing stricture or recurrence from an incomplete myotomy.

closure risks narrowing the esophageal lumen, then diverticuloplasty may be a useful technique.

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Myocardial Protection by Blood Cardioplegia and Warm Reperfusion in Heart Transplantation

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We describe the technique of blood cardioplegia delivery as we routinely use it in clinical heart transplantation. This technique needs a specific circuit. Perfusion of a first dose of blood cardioplegia is immediately started on the arrival of the graft in the operating room. Cardiac reperfusion of a half-dose of blood solution without potassium is performed each 20 minutes. Myocardial warm reperfusion is started at the end of the aortic suture. This technique of blood cardioplegia and warm reperfusion during heart transplantation provided an improvement in heart preservation when compared with standard crystalloid solution.

(Ann Thorac Surg 1992;53:525–6)

Blood cardioplegia and warm reperfusion have demonstrated enhanced myocardial protection in standard open heart operations [1–4]. Since January 1989, when we introduced blood cardioplegia in our heart transplantation program, more than 300 grafts were preserved with this method. Cardiac recovery was significantly better with blood cardioplegia when compared with standard crystalloid myocardial protection. We described herein the technique of blood cardioplegia delivery as we routinely use it in clinical heart transplantation.

Technique

Cardioplegia Induction on the Donor Graft

Harvesting of the donor graft begins with a perfusion of cold crystalloid solution (Plegisol; Abbott Laboratories, North Chicago, IL) (Table 1) infused through an aortic catheter fixed to the donor's aorta with a pursestring of 4-0 polypropylene suture. This catheter is left in place after cardiectomy. The heart is excised and then placed in a sterile plastic box with cold saline solution (Ringer solution) and transferred in an isothermic container maintaining a constant temperature between 4° to 6°C without ice contact (Transplanthermm; Cardicorp SA).

Blood Cardioplegia Circuit

The blood cardioplegia technique needs a specific circuit (Fig 1). A disposable blood cardioplegia delivery system (Dideco-Shiley Inc) with a separate in-line heat exchanger to obtain and maintain the temperature of the perfusate at an appropriate level is used.

The circuit is connected to the oxygenator (bubble or membrane) at the coronary outlet. A soft bag (1.2 L) contains the cardioplegic solution and serves as a bubble trap. The heat exchanger is of the pediatric type, with a low priming volume (57 mL). A temperature probe connector allows monitoring of the cardioplegic solution temperature. An injection port allows drug administration. The circuit is connected to the cardiotomy reservoir to facilitate its debubbling.

Blood Cardioplegia Administration

In the operating room, on arrival of the graft, cardiopulmonary bypass is immediately started on the recipient. A first dose of blood cardioplegia is prepared and stored in the soft bag of the extracorporeal circuit during the excision of the recipient's heart. The composition of blood cardioplegia is shown in Table 1. The solution is recirculated in the closed circuit to lower its temperature to 8° to 10°C. After deairing of the donor's heart and aorta, infusion of blood cardioplegia is started through the aortic catheter used previously for crystalloid cardioplegia dur-

Table 1. Composition of Cardioplegic Solutions

Component	Plegisol	Blood Cardioplegia	Blood Reperfusion
Na (mEq/L)	110	140	140
K (mEq/L)	16	26–30	5–10
Ca (mEq/L)	2.4	0.6–1	0.6–1
Bicarbonate	10	. . .	. . .
pH	7.5–7.8	7.5–7.7	7.5–7.7
Osmolarity	330	360	360
Temperature (°C)	4	10	34
Hematocrit	. . .	0.20	0.20
CPD (mL)	. . .	20	20
THAM (mL)	. . .	50	50
TNT (mg)	. . .	. . .	3
Glutamate (millimoles)	. . .	. . .	26

CPD = citrate-phosphate-dextrose; THAM = tromethamine; TNT = trinitrine.

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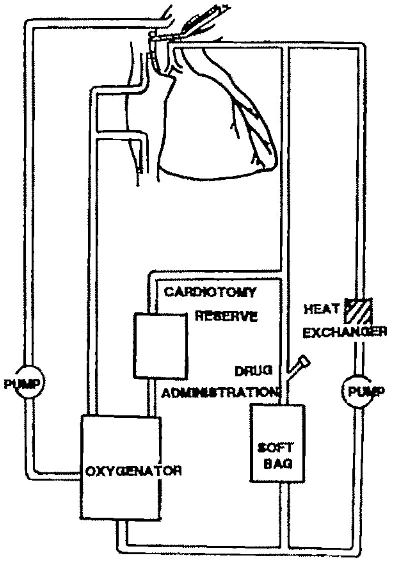

Fig 1. Blood cardioplegia circuit.

ing heart procurement (Fig 2). The solution is injected at a flow rate of 150 mL · min^{-1} · m^{-2}. The total amount of blood cardioplegia solution is delivered during a period of 3 minutes. The body temperature of the recipient is lowered to 31° to 34°C. Cardiac reperfusion of a half-dose of blood solution (75 mL · min^{-1} · m^{-2} during 3 minutes) without potassium is performed each 20 minutes.

Myocardial Warm Reperfusion

Rewarming of the recipient's body temperature starts during the accomplishment of aortic anastomosis. Myocardial warm reperfusion (see Table 1) is started at the end of the aortic anastomosis. The same volume as the initial dose is delivered at 150 mL · min^{-1} · m^{-2} during 3 minutes. During this time, residual air from cardiac cavities is evacuated with a left ventricular vent and through a large needle introduced directly in the left ventricular cavity through the apex.

When warm reperfusion is finished and after deairing of the heart, the aortic clamp is removed and residual microbubbles are sucked from the aorta.

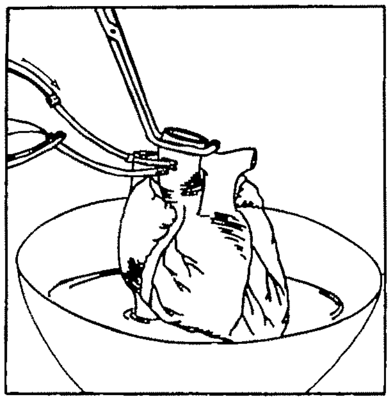

Fig 2. Infusion of blood cardioplegia through the aortic catheter.

Table 2. Comparison of Crystalloid Cardioplegia Versus Blood Cardioplegia

Variable	Crystalloid Cardioplegia (n = 50)	Blood Cardioplegia (n = 50)	p Value[a]
Spontaneous defibrillation	2 (4%)	42 (84%)	<0.05
Sinus rhythm	36 (72%)	46 (92%)	<0.05
Ventilation duration (h)	68 ± 81	40 ± 35	<0.05
Isoprenaline duration (h)	117 ± 59	107 ± 106	NS
Dopamine duration (h)	166 ± 74	130 ± 90	<0.05
Dopamine (3rd day) mean dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	8.4 ± 3.8	6.8 ± 3.8	<0.05
Cardiac index (7th day) >3.5 L · min^{-1} · m^{-2}	15 (34%)	21 (50%)	NS
Early mortality (10th day)	8 (16%)	6 (12%)	NS
Hospital mortality (30th day)	10 (20%)	7 (14%)	NS

[a] Statistical analysis was performed with Student's t test for comparisons between continuous variables and χ^2 for comparisons of categorical variables. Values of p less than 0.05 were considered statistically significant.

NS = not significant.

Comment

This technique of blood cardioplegia and warm reperfusion provided an improvement in heart preservation when compared with standard crystalloid solution. Retrospective comparison of two matched cohorts of 50 patients receiving either crystalloid cardioplegia or blood cardioplegia and warm reperfusion revealed that recovery of cardiac function was significantly better in the group receiving blood cardioplegia. Cardiac function was clinically assessed by the occurrence of rhythm disturbances, hemodynamic data, subsequent use of inotropic drugs, and duration of ventilatory support (Table 2). We therefore recommend the systematic use of blood cardioplegia and warm reperfusion in heart transplantation.

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New Technique in the Transfer of an Anomalously Originated Left Coronary Artery to the Aorta

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A 21-month-old girl with an anomalous origin of the left coronary artery underwent a transfer of the left coronary artery to the aorta using a new technique of coronary prolongation. Because the anomalous left coronary artery arising from the left anterior aspect of the pulmonary trunk was too short to reach the aorta, a simple transfer of the left coronary artery to the aorta was deemed impossible. Therefore, a transfer was performed with the help of a coronary prolongation technique using the cuff of the pulmonary trunk and an aortic flap. The new route of the left coronary artery was established anterior to the pulmonary trunk. Postoperative angiography showed a patent left coronary artery without any narrowing or kinking, as well as an improved contractility of the left ventricle. Postoperative cardiac scintigraphy showed a decreased ischemic area. This technique is thus considered applicable when the orifice of the anomalous left coronary artery is too distant from the aorta for a direct anastomosis.

(Ann Thorac Surg 1992;53:527–9)

In the surgical treatment of an anomalous origin of the left coronary artery (LCA) from the pulmonary trunk, the establishment of a two-coronary-artery system is desirable [1, 2]. Among the variety of surgical techniques, a transfer of the LCA to the aorta is thought to be an ideal method for long-term patency and adequate blood supply. However, this procedure is sometimes difficult to perform when the ostium of the LCA is greatly separated from the aorta. The new technique presented herein is believed to make a transfer possible in some cases in which other methods have been indicated previously.

A 16-month-old girl with a history of congestive heart failure was admitted to our hospital on April 18, 1988. There was a grade 3/6 regurgitant systolic murmur at the apex. An electrocardiogram showed left atrial overload, left ventricular hypertrophy, depressed R waves in leads V_1 and V_2, and abnormal Q waves in leads I, aV_L, and V_3 through V_6. Echocardiography showed fusion of the anterolateral mitral commissure and a moderate degree of mitral regurgitation due to a prolapse of the anterior leaflet. A thallium 201 cardiac scintigram revealed a perfusion defect in the anteroseptal and apical areas. Cardiac catheterization showed an oxygen step-up in the pulmonary trunk, and the pulmonary/systemic blood flow ratio was 1.6. Left ventriculography showed grade 3 mitral regurgitation and an ejection fraction of 0.52. Coronary angiography showed a dilated right coronary artery originating from the aorta and a LCA retrogradely well opacified and draining into the pulmonary trunk (Fig 1).

The patient was registered as a nonurgent case on the waiting list because of her stable clinical condition and was not operated on until she was 21 months old and had a body weight of 9.1 kg. However, we now believe that the operation should have been performed immediately after diagnosis, because her condition had been essentially life-threatening.

Under total cardiopulmonary bypass with moderate hypothermia, the aorta was cross-clamped. Both anterolateral mitral commissurotomy and annuloplication in the posteromedial commissural region were performed through a left atriotomy. Next the pulmonary trunk was incised and the orifice of the LCA was recognized in the anterior pulmonary sinus. The LCA was excised with a wide and long cuff and was dissected down near its bifurcation (Fig 2A). The defect in the pulmonary trunk was closed with an autologous pericardial patch. The aorta was incised to make a swinging-door–shaped flap (Fig 2B). The cuff of the LCA was sutured onto the aortic flap with a continuous 6-0 polydioxanone suture. Thus, a new route was established anterior to the pulmonary trunk.

The postoperative course was uneventful. Progression of R waves in leads V_1 through V_3 on the electrocardiogram and decreased ischemic area in the thallium 201 cardiac scintigram were recognized. The left ventriculogram performed on the 35th postoperative day showed both improved contractility and grade 2 mitral regurgitation. The aortogram showed good flow of the LCA without any narrowing or kinking (Fig 3). Despite residual mitral regurgitation, the patient has been doing well under supervised medical treatment 2 years after the operation.

Comment

The distance between the orifice of the anomalous LCA and the aorta is the key for a transfer of the anomalous LCA [3]. There have been some reports that have stated

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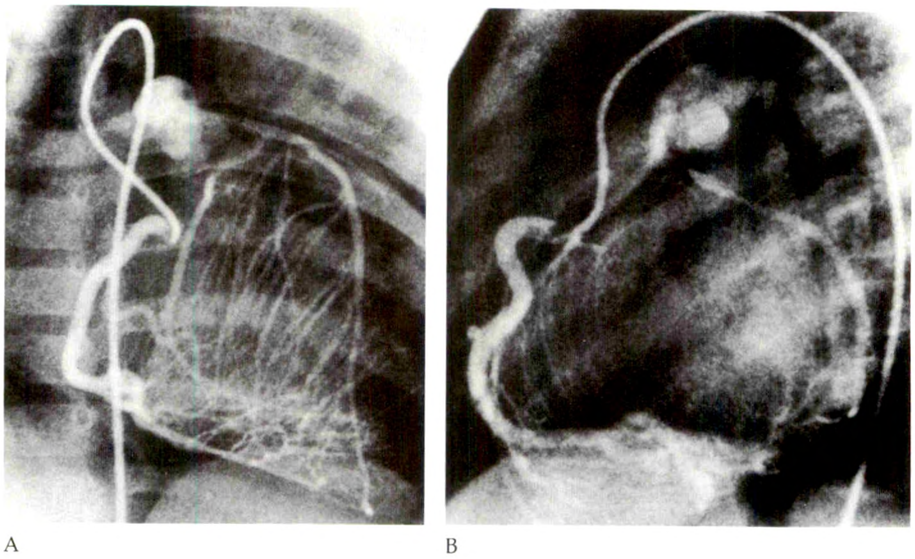

Fig 1. Preoperative coronary angiograms demonstrating the right coronary artery arising from the aorta and retrograde filling of the anomalous left coronary artery draining into the anterior wall of the main pulmonary artery. (A, right anterior oblique view; B, left anterior oblique view.)

that excising the LCA with a wide cuff resulted in easy transfer without any kinking in patients with an LCA arising from the *posterior* aspect of the pulmonary trunk [4]. However, even if this technique is used, transfer still appears to be difficult when the LCA arises from the *lateral* aspect of the pulmonary trunk. Therefore, an intrapulmonary tunnel patch procedure [5] or subclavian-coronary artery anastomosis [6] may be indicated in such a case.

In our patient, the LCA arose from the *left anterior* aspect of the pulmonary trunk; thus the intrapulmonary tunnel patch procedure also appeared to present difficulties. Subclavian-coronary artery anastomosis was possible in this case, but a dissection of the left subclavian artery through the median sternotomy, which was necessary for concomitant mitral repair, proved to be difficult. Therefore, transfer of the LCA by the new technique described herein was chosen. A modification of this method, making a route posterior to the pulmonary trunk, may be also possible in patients with the LCA arising from the *lateral* aspect of the pulmonary trunk.

In conclusion, this technique is considered to be very useful for transfer of the anomalous LCA to the aorta when the ostium of the LCA is greatly distant from the aorta.

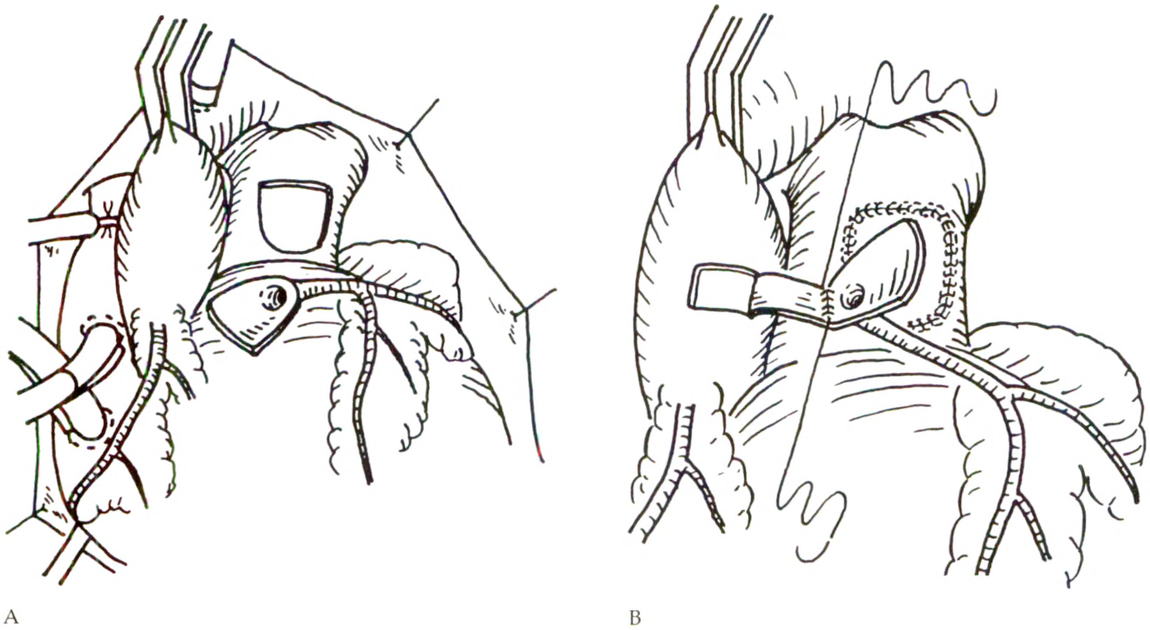

Fig 2. Technique used to transfer the anomalous left coronary artery to the aorta. The anomalous left coronary artery was excised with a wide and long pulmonary cuff (A). After the defect in the pulmonary trunk was closed with an autologous pericardial patch, the cuff of the left coronary artery was sutured onto the aortic flap (B). The anterior half of the prolonged segment of the LCA was formed by the pulmonary cuff, and the posterior half by the aortic flap.

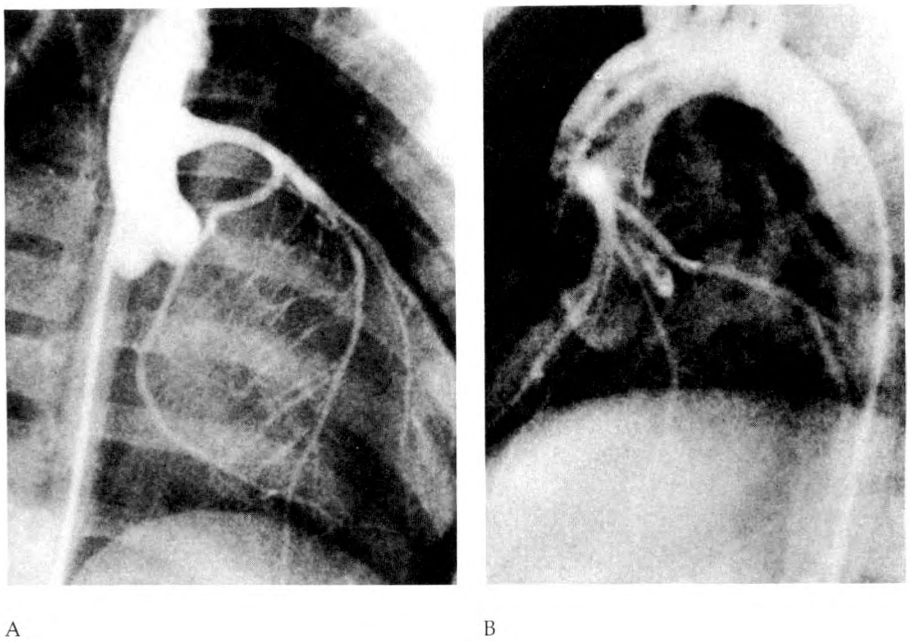

Fig 3. Postoperative aortogram shows good flow of the left coronary artery without any kinking or stenosis. (A, right anterior oblique view; B, left anterior oblique view.)

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Autologous Fibrin Glue From Intraoperatively Collected Platelet-Rich Plasma

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A simple and inexpensive means of creating autologous fibrin glue is described that avoids the potential disadvantages of conventionally obtained material. This improvement may allow more widespread use of fibrin glue for operative bleeding.

(Ann Thorac Surg 1992;53:530–1)

Widespread use of fibrin glue has been slowed by fears of virus transmission associated with the use of banked homologous cryoprecipitate. The use of autologous cryoprecipitate has been proposed to eliminate the risks of viral transmission [1]. The implementation of a program for the preparation of autologous cryoprecipitate has proved to be complex, logistically unwieldy, and expensive. Recently, a novel method for the preparation of autologous fibrin glue from autologous plasma, bovine thrombin, and calcium chloride has been described [2]. We propose a modification of that technique that entails the use of platelet-rich plasma, which is routinely collected preoperatively at the onset of many open heart operations.

Technique

Using a Plasma Saver device (Haemonetics, Braintree, MA), blood from patients undergoing open heart procedures is generally centrifuged at 3,000 rpm for 15 minutes. The platelet-rich plasma is separated from red corpuscles during the process and is conventionally administered intravenously as needed intraoperatively or postoperatively. In the currently proposed modification of the original technique [2], 20 mL of the plasma is removed and stored in a syringe. A second syringe is filled with a mixture of 0.5 mL of 10% calcium chloride solution (LyphoMed Inc, Rosemont, IL) and 10,000 units of bovine thrombin (Parke-Davis, Morris Plains, NJ). The amount of fibrin glue can be increased by removing additional platelet-rich plasma and adding 500 units of bovine thrombin for each milliliter of plasma used. The contents of the two syringes are injected onto the target surface and a fibrin clot is formed.

Comment

We tested this technique in an rabbit model in which 0.5-cm incisions were created in the liver and spleen with a number 10 scapel blade. Untreated incisions stopped bleeding at approximately 100 seconds (range, 70 to 180 seconds). In wounds treated with conventionally prepared fibrin glue from our blood bank, bleeding stopped 25 seconds later (range, 15 to 44 seconds). In incisions covered with platelet-rich plasma taken from human donors using the technique described in this report, bleeding stopped at 16 seconds (range, 6 to 29 seconds). With the number of experiments performed, no statistically significant difference between cryoprecipitate prepared fibrin glue and that derived from platelet-rich plasma was observed. Dose-response analysis of platelet-rich plasma efficacy at different times after collection failed to reveal any significant degradation under 6 hours of storage. Use of differing thrombin concentrations between 2,000 and 5,000 U/mL also did not reveal any significant differences.

This technique has been used in a variety of open heart procedures. The fibrin clot resulting from this technique does not appear as viscous as conventional glue and appears to work best on large raw surfaces such as the superior mediastinum or dissected areas after reoperations. Serious oozing from specific bleeding sites should be temporarily stopped or covered by an additional coagulating compound before application of platelet-rich plasma to allow the material to form a stable clot. Contraindications to use of platelet-rich plasma are limited. Patients with allergies to bovine materials should be excluded from this technique. In addition, the risk of tamponade may be theoretically increased; however, this problem is true whenever clotting agents are used within the pericardial cavity. The major advantages of this technique are (1) the minimal cost of platelet-rich plasma prepared in this fashion, (2) the convenience of obtaining

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this material from an already present source within the operating theater, and (3) the autologous nature of the fibrin glue. Without the risk of virus transmission and logistics of obtaining autologous banked cryoprecipitate, more surgeons can take advantage of the beneficial effects of fibrin glue.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1994 may begin the recertification process in 1992. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1992. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Julian's Reintroduction of Milton's Operation

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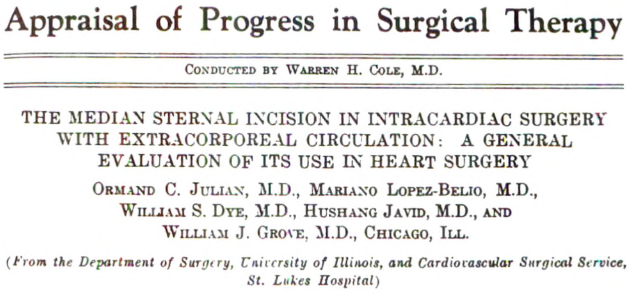
Four years after the first successful open heart operation in 1953, most cardiac surgeons were using bilateral anterior thoracotomy. This tedious, time-consuming, complication-prone, painful procedure was abandoned only after Julian and associates demonstrated the marked superiority of median sternotomy. Although median sternotomy was described by Milton in 1897, it was a seldom-used procedure at the time of Julian and associates' publication in 1957. The present-day routine use of median sternotomy for virtually all cardiac operations is a testimonial to the foresight and practicality of Julian's experience.

(Ann Thorac Surg 1992;53:532–3)



Appraisal of Progress in Surgical Therapy

CONDUCTED BY WARREN H. COLE, M.D.

THE MEDIAN STERNAL INCISION IN INTRACARDIAC SURGERY WITH EXTRACORPOREAL CIRCULATION: A GENERAL EVALUATION OF ITS USE IN HEART SURGERY

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WILLIAM S. DYE, M.D., HUSHANG JAVID, M.D., AND
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Median sternotomy was succinctly described by Milton in 1897. After cadaver dissection and animal experimentation, Milton performed the first median sternotomy to remove massive tuberculous lymph nodes compressing the anterior mediastinum [1]. For his second case in 1901 [2], a foreign body was successfully removed from the trachea only to have the patient succumb to overwhelming sepsis. In the 1920's Sauerbruch [3] employed "Milton's operation" (median sternotomy) to effectively approach the thymus and the anterior mediastinum. Holman and Willett [4] advocated median sternotomy for pericardiectomy for chronic constrictive pericarditis in 1950, and others expanded the use of median sternotomy as an approach to heart wounds [5], mediastinal masses [6], and thymectomy [7].

In 1953, Shumacker became the first surgeon to recommend median sternotomy as the preferred approach for elective heart operations, using this procedure successfully for closed valvulotomy for isolated pulmonic stenosis [8]. That same year marked the advent of open heart surgery with the first successful use of the pump-oxygenator by Gibbon [9] to repair an atrial septal defect. However, because of the fear of inadequate exposure as well as for safe caval cannulation, virtually all early cardiac surgeons preferred bilateral anterior thoracotomy performed from axilla to axilla [10].

In October 1957, in *Surgery*, Julian and associates [11] captured the attention of the rapidly growing numbers of cardiac surgeons with their report on the "Median sternal incision in intracardiac surgery with extracorporeal circulation: a general evaluation of its use in heart surgery." In 4 patients, they used a longitudinal sternum-splitting incision, largely to circumvent pulmonary complications secondary to the transverse incision. These authors demonstrated that a vertical incision in the sternum provided the same access for complete exposure of the venae cavae as bilateral anterior thoracotomy. Julian's method consisted of a transverse low collar incision over the sternal manubrium designed to diminish the high neck scar. This was joined by a long limb of a T to expose the sternum for

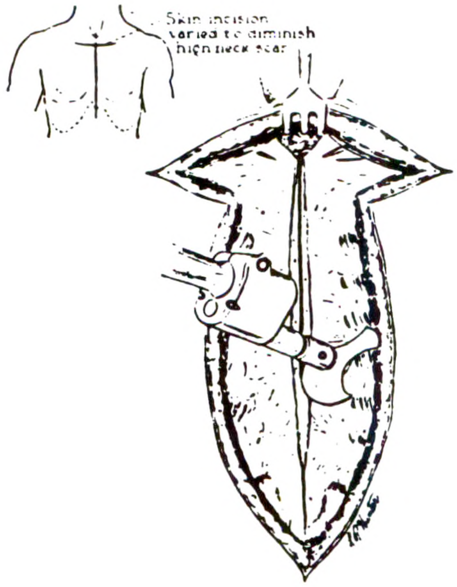

Fig 1. Skin incision is shown in modified T *form used to minimize scar. Use of power of oscillating type is recommended. (Reproduced from Julian OC, Lopez-Belio M, Dye WS, et al. The median sternal incision in intracardial surgery with extracorporeal circulation: a general evaluation of its use in heart surgery. Surgery 1957;42:753–61, by permission.)*

Address reprint requests to Dr Dalton, 777 Hemlock St, Box 98, Macon, GA 31208.

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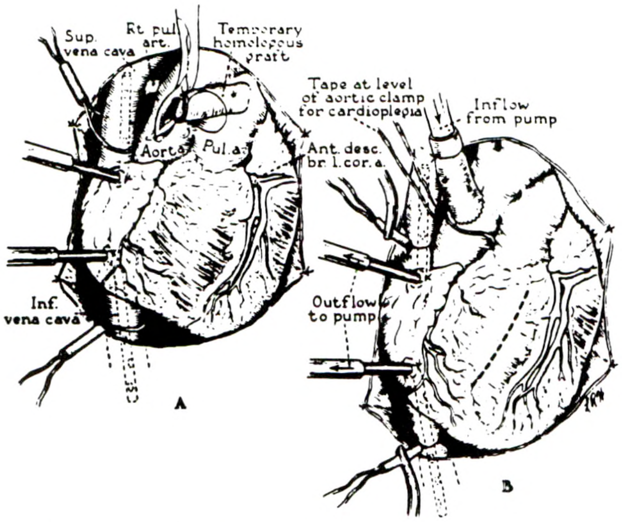
Sup. vena cava
Rt pul. art.
Temporary homologous graft
Tape at level of aortic clamp for cardioplegia
Inflow from pump
Aorta
Pul.a.
Ant. desc. br. l. cor. a.
Inf. vena cava
Outflow to pump
A
B

Fig 2. Diagrammatic representation of the central connections to the pump-oxygenator. (Reproduced from Julian OC, Lopez-Belio M, Dye WS, et al. The median sternal incision in intracardial surgery with extracorporeal circulation: a general evaluation of its use in heart surgery. Surgery 1957;42:753–61, by permission.)

midline division (Fig 1). The sternum was then incised using the Stryker saw. Cannulation, both arterial and venous, was much simpler, and arterial inflow perfusion was facilitated by applying a temporary homologous graft to the ascending aorta (Fig 2).

"A marked reduction in operating time was . . . noted" with "at least 40 minutes . . . saved in comparison to the time required to open and close the bilateral thoracotomy incision" [11]. The incision provided excellent global exposure of the heart, the aorta, and the pulmonary artery. In particular, decreased lung trauma was also a notable attribute. Importantly, "the intrapericardial isolation of the superior vena cava for encirclement with tape is simpler than with other incisions" [11].

The sternum was securely closed with wire sutures in 3 of the 4 patients. Unfortunately, patient 2 died on the 12th postoperative day, and death was attributed to wound disruption. Significantly the sternum had been closed with absorbable sutures for reasons not stated. In summary, the important benefits derived from the midline incision were marked shortening of the time of obtaining exposure, shortening closing time, and the ability of the anesthetist to manually inflate the lungs during perfusion to reduce pulmonary trauma and prevent atelectasis.

In 1957, the principal indication for open heart operation was congenital heart disease, and the majority of patients were cyanotic. Julian and associates pointed out that "lack of lung damage during surgery may be the deciding factor in the cyanotic group of patients" and emphasized that "the major benefit to accrue from this approach . . . is the avoidance of essentially all trauma to the lung and the freedom from postoperative splinting of the chest due to pain" [11].

After the report by Julian and associates, the employment of bilateral anterior thoracotomy sharply declined and the increased use of median sternotomy rapidly became apparent. The change was dramatic, and due to the clarity and succinctness of Julian's presentation, it was conspicuous to all cardiac surgeons that median sternotomy was the approach of choice. In the ensuing 34 years, this has remained unchanged. With the advent of coronary bypass operation in 1967, median sternotomy became one of the most commonly performed procedures in the world. The amount of patient suffering and complications avoided by the abandonment of bilateral anterior thoracotomy for cardiac operations is truly incalculable. All cardiac surgeons are indebted to Julian for this historic contribution in the resurrection of an operation that was first described 60 years before his 1957 publication. As Julian suggested, "trial of this approach encourages its routine use" [11].

We acknowledge the photographic assistance of Paula Huffmaster.

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Esophageal Perforation: A Continuing Challenge

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Perforation of the esophagus remains a diagnostic and therapeutic challenge. Currently, the most common cause of perforation is instrumentation of the esophagus, and the incidence of esophageal perforations has increased as the use of endoscopic procedures has become more frequent. Diagnosis depends on a high degree of suspicion and recognition of clinical features, and is confirmed by contrast esophagography or endoscopy. Outcome after esophageal perforation is dependent on the cause and location of the injury, the presence of underlying esophageal disease, and the interval between injury and initiation of treatment. Reinforced primary repair of the perforation is the most frequently employed and preferable approach to the surgical management of esophageal perforations. Nonoperative management consisting of antibiotics and parenteral nutrition is particularly successful for limited esophageal injuries meeting proper selection criteria.

(Ann Thorac Surg 1992;53:534–43)

Despite the many advancements made in thoracic surgery, the management of patients with esophageal perforations remains problematic and controversial. Although results have improved since the advent of broad-spectrum antibiotics and better nutritional support, esophageal perforation still represents a continuing challenge to the clinician. The diagnosis is often difficult to make, as clinical findings may be subtle and mimic other disorders, yet delay in diagnosis and initiation of treatment results in potentially high morbidity and mortality. Further, the low frequency of occurrence of esophageal perforation leads to a lack of experience for most individual surgeons. In addition, no single method of therapy is universally agreed on as ideal, and the frequent presence of underlying esophageal disease complicates management.

Historical Notes

The clinical features of esophageal perforation have long been recognized and have been extensively described in the literature. Although mention is made of an esophagocutaneous fistula secondary to perforation in the Smith papyrus dating from 2,500 BC [1], the first report of spontaneous esophageal perforation was made by Boerhaave [2] in 1724. In 70 pages of clinical and pathological observations, Boerhaave described the distal esophageal rupture that occurred in the High Admiral Baron de Wessenaer in association with forceful vomiting after overindulgence in food and drink. Although Frink [3] had treated a patient with esophageal rupture by surgical drainage in 1941, it was not until 1944 that the first surgical repair after spontaneous perforation was attempted by Collins and associates [4], laying the foundation for the first reported successful repairs by Barret [5] and by Olsen and Clagett [6] in 1947. In that same year, Brewer and Burford [7] also reported the successful surgical repair of a traumatic esophageal perforation. Five years later, Satinsky and Kron [8] reported the first successful esophagectomy after a perforation. Over the subsequent 40 years, the incidence of esophageal perforation has increased [9], iatrogenic causes of esophageal perforations have become more prevalent than spontaneous ruptures, and different management techniques have evolved.

Etiology and Location

The causes of esophageal perforation are as follows:

I. Instrumentation/iatrogenic
  A. Intraluminal
    1. Esophagoscopy
    2. Bougienage
    3. Pneumatic dilation
    4. Sclerosis of esophageal varices
    5. Placement of intraesophageal tubes (nasogastric, Sengstaken-Blakemore, prostheses)
    6. Endotracheal tube placement
  B. Extraluminal
    1. Mediastinoscopy
    2. Intraoperative injury
      a. Thyroid resection
      b. Leiomyoma enucleation
      c. Proximal gastric vagotomy
      d. Pneumonectomy
    3. Radiation therapy

II. Traumatic
  A. Blunt
  B. Penetrating
  C. Ingestion of caustic substance

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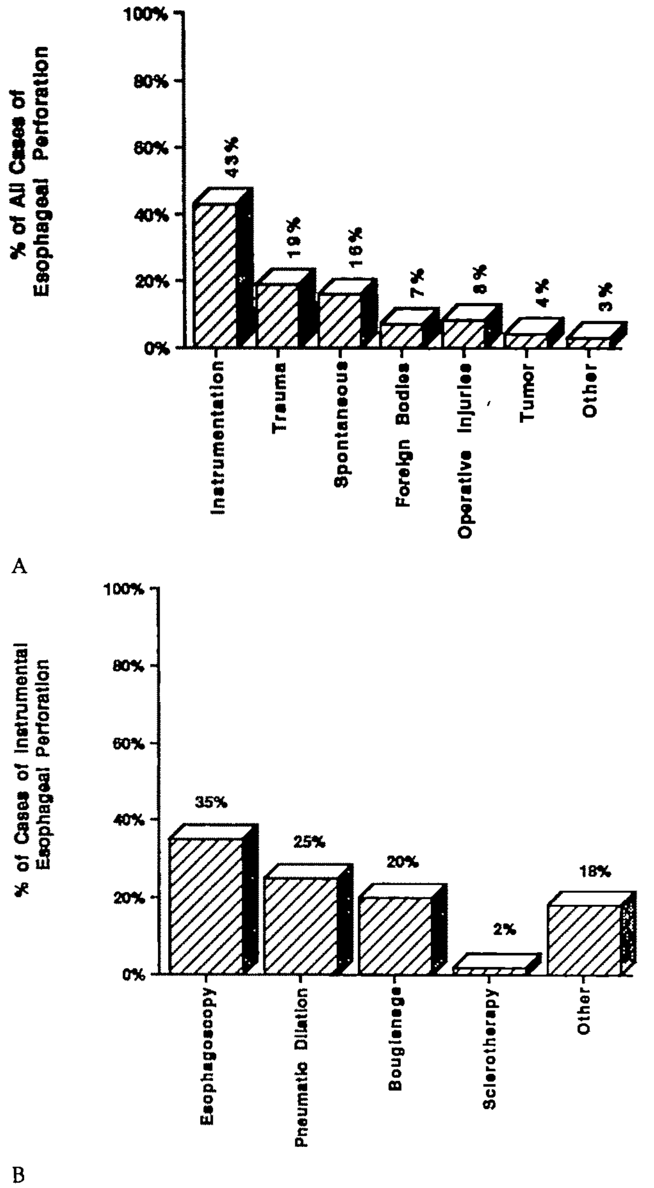

Fig 1. (A) Cause of 511 cases of esophageal perforation in recent series, and (B) types of instrumental perforations among those cases. (Data from references 49–51, 55, 72, 112, and 113.)

III. Spontaneous (barogenic)
  A. Postemetic
  B. Other

IV. Ingestion of foreign body
V. Tumor
VI. Surrounding infections

Their relative frequency from reported series is depicted in Figure 1, and the relationship of cause to location is shown in Figure 2.

Instrumental esophageal perforation occurs in about 1/10,000 upper gastrointestinal endoscopies. In a 1974 American Society of Gastrointestinal Endoscopy survey [10] of 211,410 procedures, perforation occurred in 0.03% of all simple upper endoscopies and in 0.25% of procedures involving bougienage. With an incidence ranging from 1% to 10% [11, 12], pneumatic dilation for achalasia is associated with a fourfold greater risk of perforation than myotomy [13], and this may be related to patient malnutrition [14] or high-compliance balloons [15]. Endoscopic sclerosis of esophageal varices leads to perforation in 1% to 4% of cases [16–19] and the result may be in part dependent on the type and volume of sclerosing agent employed [18, 19], although this concept is disputed by Korula and colleagues [20]. Esophageal perforation can also occur during placement of nasogastric tubes [21, 22], Sengstaken-Blakemore tubes [23, 24], endoesophageal prostheses [25–27], and endotracheal tubes [28–30].

The area at greatest risk for instrumental injury is the cricopharyngeal region of the cervical esophagus. At Lannier's triangle, formed by the constrictor pharyngeus and the cricopharyngeus muscles at the level of the C-5 and C-6 vertebrae, the posterior esophageal mucosa is covered only by fascia. The risk of perforation in this area is further increased by hyperextension of the neck and the presence of kyphosis or cervical vertebral spurs [31].

The next most common areas of instrumental esophageal perforation are the relatively narrow but fixed portions at the distal esophagus just proximal to the hiatus and near the aortic arch and left main bronchus. Other areas at risk include portions of the esophagus just proximal to obstructing processes, portions with extensive carcinomas, and portions at biopsy sites.

Intraoperative injury to the esophagus can occur in areas where an operative procedure is in close proximity to the esophagus. Intraoperative esophageal injury has been reported after anterior cervical spine operations [32, 33], mediastinoscopy [34], thyroid resection [1], leiomyoma enucleation [1], proximal gastric vagotomy [35–38], hiatal hernia repair [35, 39, 40], and pneumonectomy [41].

Perforations from either blunt or penetrating trauma occur primarily in the neck, whereas perforations from ingested foreign bodies or caustic substances are more likely to be intrathoracic. Spontaneous esophageal perforations are barogenic in origin, resulting from a sudden rapid rise in intraesophageal pressure such as can occur with forceful vomiting, childbirth, weight lifting, or blunt abdominal trauma. Barogenic perforations usually occur on the left wall of the distal supradiaphragmatic esophagus, extending into the pleural cavity in 80% of cases [1, 42, 43]. Other less common causes such as perforations of esophageal carcinomas [44–47] and perforations from surrounding infections, especially in immunocompromised patients [48], can occur anywhere in the intrathoracic esophagus.

The association of underlying esophageal disease with esophageal perforation is depicted in Figure 3. Among 147 patients in seven large series of esophageal perforation from a variety of causes [23, 49–54], no underlying esophageal pathology was present in 40%. Benign strictures and anatomic lesions such as diverticula were most commonly associated with perforations, usually instrumental in origin, whereas tumors or achalasia occurred less frequently.

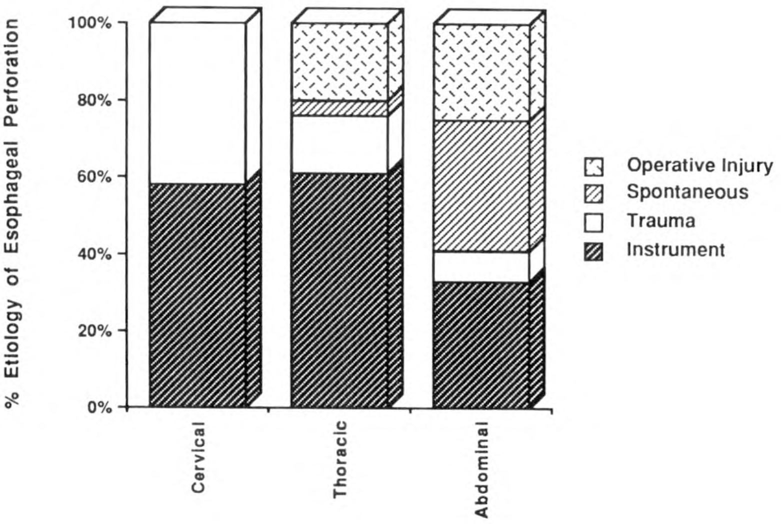

Fig 2. Relationship of cause to location of esophageal perforations in recent series. (Data from references 49, 51, 55, 112, and 113.)

Clinical Features

Diagnosis of esophageal perforation can be difficult, as the presentation is often nonspecific and is easily confused with other disorders such as peptic ulcer disease, pancreatitis, myocardial infarction, dissecting aortic aneurysm, pneumonia, or spontaneous pneumothorax [55, 56]. The signs and symptoms of esophageal perforation depend on the location and cause of the perforation and the interval since the perforation occurred.

Cervical perforations most often occur posteriorly where the esophageal wall is thin. Dissection through the retroesophageal space allows spread of contamination to the mediastinum over time, but attachments of the esophagus to the prevertebral fascia may limit lateral spread. Thus, early signs of cervical esophageal perforation include neck stiffness and a dull neck ache, regurgitation of bloody material, and the finding of cervical subcutaneous emphysema. Inflammatory changes in the neck may not develop for several hours, with signs of systemic sepsis often not occurring for up to 24 hours.

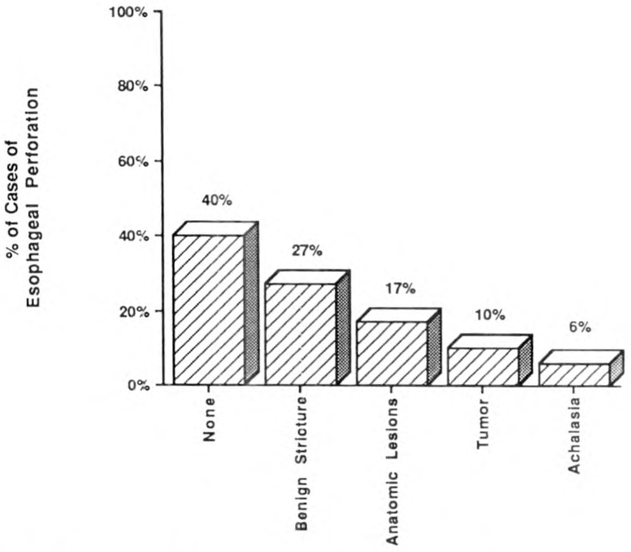

Fig 3. Underlying esophageal disease in patients with esophageal perforation. (Data from references 23 and 49 through 54.)

In contrast, perforations of the thoracic esophagus result directly in mediastinal contamination, leading to a more rapid development of pneumomediastinum and mediastinitis than after cervical perforations. The thin mediastinal pleura is usually ruptured by the inflammatory process, producing contamination of the pleural space and a pleural effusion. Gastric contents and fluids are then drawn into the pleural space by the negative intrathoracic pressure [41], resulting in further inflammation and fluid sequestration, hypovolemia, and the early appearance of tachycardia and systemic sepsis. Chest pain and subcutaneous emphysema are usually present, and dyspnea is often prominent even in the absence of pneumothorax.

Intraabdominal esophageal perforations occur into the free peritoneal cavity and result in peritonitis. A dull retrosternal ache in association with epigastric pain radiating to the shoulders is characteristic because of the relationship of the intraabdominal esophagus to the diaphragm. Systemic signs such as tachycardia, tachypnea, and fever develop early, with progression to sepsis and shock occurring within hours.

Diagnosis

Prompt diagnosis of esophageal perforations is essential, as the incidence of complications and the rate of mortality are dependent on the interval between the perforation and the initiation of treatment. The presence of neck, chest, or abdominal pain after upper gastrointestinal endoscopy should always raise the suspicion of an esophageal perforation and necessitates further study to eliminate the possibility that perforation has occurred.

Plain film findings vary according to the location and cause of the perforation, as well as the interval between injury and radiographic examination [57]. Findings of cervical or mediastinal emphysema, pneumothorax or pneumopericardium, pleural effusion, or subdiaphragmatic air are all suggestive of a perforated esophagus and warrant further diagnostic study with contrast esophagograms. The presence of food particles or a pH of less than 6.0 in the pleural fluid aspirate is virtually diagnostic [58].

Noncontrast radiographic studies will be normal in 12% [57] to 33% [59] of cases of esophageal perforation, leading some authors [60] to recommend contrast studies after all endoscopic dilations. Although contrast esophagograms are the standard diagnostic procedures in cases of suspected esophageal perforation, it should be noted that the false-negative rate of these examinations can also exceed 10% [45]. Thus, "negative" studies may not completely eliminate the possibility of a perforation. When positive, contrast studies have the advantage of demonstrating the level of the perforation and the presence of extension into the pleural cavity.

The ideal contrast agent for esophagography for suspected perforation was previously the subject of some debate [61–64]. Water-soluble contrast medium is rapidly absorbed and is purported to be less irritating than barium should substantial extravasation occur [65]. Our preference is thinned barium, which may improve localization of subtle perforations [66], and it should be employed whenever a major risk of aspiration is present or whenever a concomitant respiratory tract injury or fistula is suspected. Foley and co-workers [65] recommend an initial bolus of water-soluble contrast medium and then a repeat of the study with a small amount of barium if no leak is seen.

In the patient in whom esophageal perforation is highly suspected clinically but in whom contrast esophagograms are negative, flexible esophagoscopy and computed tomography can be useful diagnostic adjuvants. Flexible esophagoscopy may currently be underutilized in the diagnosis of esophageal perforation. This method provides highly accurate localization as well as direct visualization of perforations [67]. Furthermore, results of esophagoscopy may directly influence treatment decisions, as small perforations or perforations limited to the mucosa can be expected to heal with nonoperative management in the absence of distal obstruction. In select cases, esophagoscopy can facilitate placement of a tube through the perforation for irrigation and drainage [68].

Computed tomographic findings suggestive of esophageal perforation include air in the soft tissues of the mediastinum surrounding the esophagus, abscess cavities adjacent to the esophagus in either the pleural space or the mediastinum, or the demonstration of an actual communication between the air-filled esophagus and an adjacent mediastinal or paramediastinal air-fluid collection [58]. Computed tomographic scans are also particularly useful in follow-up after initiation of therapy and in the evaluation of patients who fail to improve despite either operative or nonoperative management [69]. Localization of loculated pleural fluid collections can also allow computed tomography–directed drainage catheter placement in the postoperative setting or during nonoperative therapy [70].

Treatment of Esophageal Perforations

Once the diagnosis of esophageal perforation is established, multiple factors must be considered in selecting the appropriate therapy. The cause of the perforation, its location, the presence of underlying esophageal disease, and the interval between perforation and diagnosis are critical factors in the determination of treatment. In addition, the condition of the esophagus and the extent of soilage or injury to adjacent organs and tissues as well as the age and general condition of the patient must also be considered.

Treatment options for esophageal perforations are as follows:

1. Operative management
   a. Primary closure
   b. Reinforced primary closure
   c. Resection
   d. Drainage alone
   e. T-tube drainage
   f. Exclusion and diversion
   g. Intraluminal stent

2. Nonoperative management

The goal of any treatment modality must be to prevent further soilage from the perforation, to eliminate the infection produced by soilage, to restore the integrity and continuity of the gastrointestinal tract, and to restore and maintain adequate nutrition [26, 45, 71–74]. Consequently, the principles of operative management include debridement of all infected and necrotic tissue, secure closure of the perforation with appropriate measures to prevent leakage, correction or elimination of distal obstruction, and drainage of contaminated and infected areas. As recovery from esophageal perforation can be prolonged, provision of a route for enteral nutrition such as a jejunostomy should also be considered during any surgical procedure.

Surgical Approaches

The surgical approach is dependent on the location of the perforation. Cervical esophageal tears are best exposed through an incision parallel to the left sternocleidomastoid muscle and anterior to the carotid artery and internal jugular vein. Perforations in the upper two-thirds of the thoracic esophagus can be reached through a right posterolateral thoracotomy in the fourth or fifth intercostal space, whereas those in the lower third are best approached through a posterolateral thoracotomy in the left sixth or seventh interspace. Abdominal esophageal injuries usually require an upper midline laparotomy. Once the esophagus is exposed, localization of subtle perforations may require instillation of methylene blue into the esophageal lumen or the insufflation of air into the esophagus immersed in saline solution.

Primary Closure

Primary closure of esophageal perforations was first described nearly 50 years ago [4–6]. Primary closure, with or without tissue reinforcement, is the most frequently used and preferable approach to the surgical management of esophageal perforations. Successful repair depends on debridement of nonviable tissue and closure of the mucosa and muscle in separate layers. Closure of the mucosa with mechanical stapling devices has also been reported [75, 76]. In most instances, the mucosal layer remains healthy. However, a myotomy may be necessary to visualize the full extent of the mucosal injury and to facilitate its repair [75, 77]. Inadequate exposure and repair of the mucosal defect can predispose to leakage from the closure [77].

Late presentation or delayed diagnosis of the perforation results in further tissue necrosis and edema, and can prevent closure or even identification of a substantial muscular layer, in which case the mucosa alone is closed. The contaminated thoracic cavity should be thoroughly irrigated and debrided, with decortication of the lung if necessary. Wide external drainage consisting of Penrose drains in the neck for cervical injuries and large-bore chest tubes for thoracic esophageal perforations should be established along with nasogastric drainage. Contrast studies are usually obtained 7 to 10 days postoperatively, at which time oral intake can be resumed if no leak is demonstrated and ileus has resolved.

Primary closure is best applied to perforations in an otherwise normal esophagus. In the case of prestenotic esophageal perforation, closure alone without resolution of the obstructing process can be doomed to failure [78, 79]. Moghissi and Pender [67] reported a 100% mortality rate among 9 patients with prestenotic perforations treated by either drainage alone or primary closure. For the 14 other patients in the series in whom the stenosis as well as the perforation was addressed, there was a reduction in the mortality rate to 29%.

Reinforced Closure

The potential for breakdown or leakage from primary closure of esophageal perforations, particularly if the interval between injury and treatment exceeds more than a few hours, has led many surgeons to advocate reinforcement of the closure. In the chest, a variety of tissues have been employed to buttress the esophageal closure. A pleural flap, as suggested by Grillo and Wilkins [80], is particularly useful if local reaction has resulted in a thickened pleura. Other choices include omentum, a pedicled intercostal muscle flap [81, 82] or pericardial fat pad flap [83, 84], elevation of a flap of diaphragm [85, 86], or coverage by infolded gastric wall as a Thal patch [87, 88] or as part of an antireflux procedure if enlargement of the hiatus is necessary or underlying reflux disease is present [56]. Regardless of the type of material used, secure closure necessitates suturing the reinforcing tissue closely, as for an anastomosis, rather than just simple "tacking" [26].

Esophageal Resection

Excellent results with esophageal resection, particularly for perforations in association with malignant obstruction or massive esophageal necrosis, have been reported [46]. A transhiatal or thoracic approach can be employed, with reconstruction performed immediately or as a second-stage procedure depending on the degree of contamination and the condition of the patient. Matthews and associates [89] advocate the use of near-total esophagectomy if resection is required. They cite the ease of performing the anastomosis in the neck, the decreased necessity to use inflamed tissues in the anastomosis, and better longitudinal lymphatic clearance in support of their view.

Concomitant Treatment of Underlying Esophageal Disease

Perforation in association with functional obstruction, as in achalasia, is best treated by repair with a myotomy performed on the side of the esophagus opposite the perforation. An antireflux procedure is generally not required if the myotomy does not extend onto the gastric cardia [90]. However, a Belsey-type repair may offer the advantage of buttressing the closure of distal perforations [91]. An antireflux procedure should also be performed when perforation is associated with hiatal hernia or major reflux esophagitis.

Thoracotomy and Drainage

Drainage alone, without repair of the perforation, is sometimes deemed necessary in the face of widespread inflammation. This technique is best applied to cervical perforations, where better drainage of the surrounding tissues can be obtained than in the chest, as it does not prevent further soilage. Closure of the perforation around a 6- to 10-mm T tube, as reported by Abbott and coworkers [92], creates a controlled esophagocutaneous fistula "venting" the esophagus. This technique may be useful when the security of an attempted repair is in doubt or adequate tissue to reinforce the closure is not available. Intraluminal tubes or stents have also been used successfully to treat perforations through carcinomas or in association with tracheoesophageal fistulas [93–96].

Exclusion and Diversion

Urschel and others [74, 97–99] have described exclusion/diversion techniques in the treatment of complicated esophageal perforations. Exclusion and diversion involves suture of the perforation, if possible, with wide drainage of contaminated tissues; creation of a loop or end-cervical esophagostomy; division or suture of the gastroesophageal junction; and creation of a gastrostomy. Advocates of these techniques claim that they are an application of principles used successfully in the treatment of perforations of other areas of the gastrointestinal tract such as perforated colonic diverticulitis [97]. Exclusion and diversion, however, commits the patient to a second major operative procedure and can create a stagnant pool in the distal esophagus with bacterial overgrowth. Gouge and associates [50] wrote that the "rationale for [the] procedure is debatable and depends on whether the benefits of preventing reflux from the distal esophagus outweighs the disadvantage of creating an obstruction in the distal esophagus." Thus, this technique should be reserved for those patients in whom other approaches are not feasible.

Nonoperative Management

In the era before antibiotics, nonoperative treatment of esophageal rupture was almost universally fatal [100]. More recently, Michel and co-authors [26] considered the findings of pneumothorax, pneumoperitoneum, pneumomediastinum, systemic sepsis, shock, or respiratory failure to be indications for operative management. These concepts are being challenged, however, as more patients with esophageal perforation are being treated without surgical intervention. The justification for this deviation from time-honored surgical therapy is fourfold: (1) most perforations are now the result of instrumentation and therefore are usually more limited, associated with less contamination, and diagnosed more promptly than spontaneous ruptures; (2) newer, more effective antibiotics have been introduced to control the infections that formerly resulted from esophageal perforation; (3) computed tomographic imaging provides the ability to more adequately drain the thoracic cavity through a percutaneous approach; and (4) there are now safe and effective forms of parenteral nutrition and alternative means of enteral nutrition. Opponents of nonoperative management recommend primary closure to decrease recovery time and minimize time of fasting and total parenteral nutrition [101].

Nonoperative therapy is best applied in the following cases: (1) instrumental perforation, especially in the cervical esophagus; (2) small perforations after bougienage of peptic strictures or achalasia or after sclerosis of esophageal varices, as the presence of periesophageal fibrosis can limit contamination of the mediastinum; and (3) esophageal perforation diagnosed several days after injury with minimal symptoms [102–108]. Nonoperative therapy is likely to fail in the presence of esophageal obstruction [109]. Based on their 30-year experience, Berry and Ochsner [110] recommended an individualized approach to the decision of operative versus nonoperative therapy.

Cameron and associates [102] and others [70, 103–108] have established criteria for nonoperative management of esophageal perforations. These criteria are as follows:

1. Recent perforation or perforation well walled off if seen late
2. Esophageal perforation well contained within the mediastinum or between the mediastinum and visceral lung pleura, with no free contrast agent escaping into adjacent body cavities
3. Cavity well drained back into the esophagus with minimal pleural soilage
4. No food intake between injury and diagnosis
5. Perforation not in area of tumor or in the abdomen or proximal to an obstructing process
6. Minimal symptoms
7. Minimal signs of clinical sepsis and minimal physiologic derangement

Patients are given nothing by mouth for usually more than 10 days, necessitating total parenteral nutrition. Broad-spectrum antibiotic therapy is administered for a minimum of 7 to 14 days. Pleural collections are drained through chest tubes or computed tomography–directed drainage catheters [70]. Nasogastric drainage is widely considered integral to nonoperative therapy, although some authors [102] report using nasogastric tubes only selectively. Nasogastric tubes placed in the region of the perforation can also be used for irrigation with either saline or antibiotic solutions as an adjunct to nonoperative treatment [68]. Failure to show signs of improvement within 24 hours of nonoperative therapy should prompt a consideration for operative intervention [25]. Computed tomographic scanning may be helpful to demonstrate undrained collections in such cases [1, 69].

Outcome

Recent series [49, 51, 72] have identified cause, location, delayed treatment, underlying esophageal disease, and type of treatment as significant risk factors for death after esophageal perforation. Examination of reported series of esophageal perforations published from 1980 through 1990 [23, 45–47, 49–53, 67, 68, 71, 111–113], the era of modern antibiotic therapy and parenteral nutrition, allows an estimate of the current risk associated with each of these factors.

Among 450 reported patients [45, 47, 49, 51, 55, 67, 111–113], iatrogenic and instrumental injuries were associated with a mortality rate of 19%, whereas spontaneous ruptures resulted in a mortality rate of 39%. Two individual series [114, 115], however, comparing outcome after treatment for spontaneous and iatrogenic perforations failed to demonstrate any significant difference in associated mortality between these two causes. Traumatic esophageal perforations in the collected series [45, 47, 49, 51, 55, 67, 111–113] had the lowest mortality rate, 9%, perhaps because of a decreased interval between perforation and treatment in the setting of multiple injury [113].

In 439 patients [7, 49, 51, 55, 67, 113], cervical tears resulted in an overall mortality rate of 6%, whereas thoracic and abdominal perforations resulted in death in 34% and 29% of patients, respectively. The diminished risk associated with perforation of the esophagus in the neck is attributed to anatomic tissue planes in this area, which prevent the rapid spread of contamination or infection [1], and to the absence of reflux of gastric contents through cervical perforations [116].

Prompt recognition and initiation of treatment of esophageal perforations has long been recognized as essential to a favorable outcome [117]. Delay in treatment of greater than 24 hours after perforation has occurred has been associated with higher rates of both complications [43] and mortality [43, 49, 51, 55, 67, 72]. Bladergroen and associates [49] reported that survival decreased from 79% to 67% and Attar and colleagues [51], from 87% to 55% if treatment was instituted more than 24 hours after the onset of symptoms. Basing a treatment plan on the interval between perforation and presentation has also been associated with reduction in mortality [72]. However, the influence of treatment delay may have dimin-

Table 1. Outcome After Treatment of Esophageal Perforation in Series Published Between 1980 and 1990[a]

Reference	Year	Primary Repair	Drainage	Resection	Exclusion and Diversion	Nonoperative	Overall Mortality[b]
Skinner et al [47]	1980	0/15	4/8	3/9	2/11	. . .	9/43 (21)
Goldstein and Thompson [112]	1982	4/23	. . .	. . .	6/9	4/12	14/44 (32)
Sarr et al [45]	1982	0/15[c]	0/13	3/8	0/3	1/8	4/47 (9)
Larsen et al [23]	1983	10/47	4/8	. . .	. . .	0/2	14/57 (25)
Ajalat and Mulder [111]	1984	0/12	1/5	0/1	1/2	3/13	5/33 (15)
Borgeskov et al [53]	1984	9/22	3/7	2/2	. . .	5/8	19/39 (49)
Radmark et al [52]	1986	1/17[d]	. . .	0/2	1/2	5/17	7/38 (18)
Brewer et al [71]	1986	9/53	0/6	0/2	0/2	0/15	9/78 (12)
Nesbitt and Sawyers [55]	1987	3/20	3/4	. . .	1/8	1/2	8/34 (24)
Moghissi and Pender [67]	1988	7/13[e]	4/5	2/11	. . .	. . .	13/29 (45)
Flynn et al [113]	1989	1/44	2/9	1/4	1/2	0/8	5/67 (7)
Gouge et al [50]	1989	0/14	0/1	1/1	2/2	. . .	3/18 (17)
Attar et al [51]	1990	5/30	7/17	2/9	4/5	. . .	18/61 (30)
Total		49/325	28/83	14/49	18/46	19/85	128/589
Mortality (%)		15	34	29	39	22	22

[a] Data are presented as number of deaths/number of patients undergoing procedure. [b] Numbers in parentheses are percentages. [c] This includes 2 patients who also underwent an antireflux procedure. [d] This includes 2 patients who also underwent myotomy. [e] This includes 5 patients who also underwent fundoplication.

ished slightly. Nesbitt and Sawyers [55] noted that if treatment was initiated within 24 hours, the mortality rate decreased from 56% to 13% during the years 1935 through 1974 but only decreased from 26% to 11.4% in the years 1975 through 1984. Decreases in mortality in patients with delayed diagnosis and treatment after esophageal perforation may be attributable to improvements in critical care, antibiotic therapy, and parenteral nutrition.

Patients with cancer of the esophagus regardless of the site of perforation appear to have increased mortality compared with patients with perforations associated with benign disease processes or no underlying esophageal disease [26, 49, 72, 114]. Further, Saaybe and co-workers [118] studied the long-term results in patients with esophageal perforations treated by repair without further surgical treatment of any underlying benign esophageal disease. They found that all patients without underlying esophageal disease remained asymptomatic up to 22 years after repair of instrumental perforations, whereas 35% of those with underlying disease had symptoms requiring reinstrumentation or reoperation.

Table 1 depicts the outcome after treatment of esophageal perforation in 13 series published between 1980 and 1990 [23, 45, 47, 50–53, 67, 71, 111–113] in which the mortality for individual procedures is reported. Among 325 patients treated with various types of primary repairs, the mortality rate ranged from 0% to 54% and averaged 15%. Gouge and associates [50] reported a 25% mortality in 158 personal and reported patients treated with primary repair versus a 6% mortality in 99 patients treated with reinforced repair. The rate of fistula formation or serious leak also decreased from 39% to 13% when the esophageal closure was reinforced. Other forms of operative management are associated with higher mortality rates in these series: exclusion and diversion, 39%; drainage only, 34%; and resection, 29%, although these increased mortality rates may also be a reflection of more complicated disease.

Nonoperative therapy resulted in a 22% mortality rate in these series (see Table 1). Previous reviews of series of esophageal perforations have reported a 25% mortality rate among 900 patients [112] in 1982 and a 38% rate among 428 patients in 1983 [23]. However, it is difficult among these cases to distinguish between election of nonoperative management as "best therapy" and nonoperative treatment because of inability to tolerate or refusal to undergo operative therapy, as multiple anecdotal reports and small series of instrumental and pediatric perforations have survival rates approaching 100% [68, 70, 103–108]. Erwall and associates [119] reported similar mortality rates between patients treated nonoperatively (12%) and those treated operatively (16%) in a series of 48 patients in whom the presence of shock or systemic symptoms, large perforations, retained foreign bodies, or esophageal malignancy were considered operative indications. Thus, patient selection according to the strict criteria listed in the Outcome section would appear to be necessary for nonoperative treatment to be successful.

Conclusion

Esophageal perforation is a potentially lethal condition resulting most frequently from instrumentation. Early diagnosis and intervention are necessary to prevent morbidity and mortality. Esophageal perforation is best treated with definitive repair including tissue reinforcement of the closure and elimination of distal obstruction.

Nonoperative therapy consisting of antibiotics and parenteral nutrition may also be appropriate in select patients.

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Responses to Minisymposium on Thoracic Surgical Education

Should We Care?—Absolutely! Do We Care?—I Do! What Should We Do?—Tough Question!

To the Editor:

The Editorial Symposium on Thoracic Surgical Education addresses issues of critical importance to our specialty [1–6]. I would like to offer some thoughts regarding thoracic surgery training. My perspective of the situation is somewhat different than that of the senior cardiothoracic surgeons whose views are presented in the symposium. I completed my residency in general surgery in 1986, and in thoracic surgery in 1988. Since that time, I have held a faculty position (Assistant Professor level) at the University of Miami School of Medicine. My clinical practice includes both cardiac surgery and general thoracic surgery. I am involved in education of medical students, general surgery residents, and thoracic surgery residents.

A multitude of factors affect our ability to attract "the best and brightest" into thoracic surgery. The number of medical school applicants has decreased over the past 10 years. There are a number of reasons why college students may not be attracted to medical education. These include factors such as declining reimbursement for health care services, increasing medicolegal risk, increasing governmental regulation, and public dissatisfaction with health care.

Currently, it takes at least 15 years to complete college, medical school, surgery residency, and thoracic surgery training. I suspect that further lengthening of training would make it unpalatable to a number of potentially good applicants. However, reducing the length of training could potentially jeopardize the educational infrastructure of the trainees.

It is my opinion that the last 2 years of general surgery training are valuable, and that this is not the optimal place for the curriculum to be shortened. It is in the final years of general surgery that residents learn much that will be helpful during cardiothoracic training. This is when they learn to deal with difficult bleeding and with shock. It is worthwhile for the residents to have experience operating on the femoral artery and the carotid artery before we expect them to deal with the pulmonary artery or the intrathoracic aorta. Certainly, a strong background in general surgery is important for esophageal operations. The cardiac surgeon utilizes general surgical training when mobilizing the gastroepiploic artery or inferior epigastric artery for myocardial revascularization. Personally, I have been well served by a strong foundation in general surgery. I believe that the time and energy spent in that period of my training was an excellent investment.

I think that most trainees in thoracic surgery are best served by a broad-based comprehensive training program, as currently required by the American Board of Thoracic Surgery. I agree wholeheartedly with Dr Orringer that it is naive to believe that intimately related intrathoracic anatomic structures can be readily separated into different subspecialties [4]. Furthermore, many residents do not know where their specific interests lie until they are well into their training. Some thoracic surgeons—and I am included here—maintain a broad spectrum of practice involving many areas of cardiac surgery and general thoracic surgery.

Changes are needed in thoracic surgery training. Appropriate changes will result in better training—not longer, shorter, harder, or easier—but better. This is essential if we are to attract "the best and the brightest" to thoracic surgery.

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6. Benfield JR. What next in cardiothoracic training? Ann Thorac Surg 1991;51:820.

Reply

Thank you for your contribution. Your major point is that the broad clinical practice of cardiac and general thoracic surgery requires the background that is provided by broad-based training programs. You share the concern of many others that reducing the length of the training programs could jeopardize education.

As we consider proposals for change in training programs, we must remember that the point in the evolution of training at which we find ourselves now is really quite good. Thoracic surgeons are very competently caring for patients whose diseases call for skills in cardiac surgery and general thoracic surgery. Change for its own sake is certainly to be avoided, but there is general agreement that improvements are needed in certain aspects of most training programs.

The question for the future is how best to adapt the existing principles of thoracic surgical training to the reality that increasing complexity of thoracic surgical practice has fostered subspecialization. In fact, each of the authors who contributed to this symposium has gained his reputation primarily as a subspecialist. However, the current leadership in thoracic surgery has also come from a background of broad-based training. Therefore, I am confident that your concern to the effect that reducing the length of training could jeopardize the excellence of education will be kept in mind as change is considered. Moreover, it is clear that there will continue to be a need for thoracic surgeons who practice the broad range of our specialty.

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The Future of Thoracic Surgery, General and Cardiac

To the Editor:

The Editorial Symposium on the future of thoracic surgery, general and cardiac, in the May 1991 issue of *The Annals* [1–6] is both timely and welcome. Being a board-certified thoracic surgeon and a member of The Society of Thoracic Surgeons, practicing in a small community for over 25 years, I want to report my observations of this question from a front-line soldier's perspective.

As a whole, the young thoracic surgeons who have settled in this area lately are well trained and good doctors. However, they do lack interest in general thoracic surgery, and I do not believe it is due only to the difference in their residency program. Perhaps the burden of cardiac surgery is so overwhelming that they found their time could be better spent by allowing the

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general thoracic surgery to be handled by pulmonologists and oncologists. Thoracic surgeons are becoming used to performing coronary artery bypass grafting as decided upon by the cardiologist or family physician without the "need" of a voice in the choice; in many instances even the decision of resectability, a surgical judgment, is made by nonsurgeons. As to those patients with nonneoplastic thoracic surgical problems, they continue to have no access to the expertise of a thoracic surgeon. Of course, this further lessens the involvement and impact of thoracic surgery and unwittingly encourages us to reduce ourselves to mere thoracic surgery technicians.

I have a suggestion and am wondering whether adding (G) or (C) to the American Board of Thoracic Surgery (ABTS) certificate would help. That is, surgeons would have ABTS (G) for preference in general thoracic, ABTS (C) for cardiac thoracic surgery, and both (G) and (C) for both categories. This designation is to be *voluntary* with the advice and consent of the residency director and/or department head. The ones who choose both (G) and (C) therefore will have to compete in practice with those (Gs) in general thoracic surgery. This way the public and the primary care providers can accurately recognize the appropriate person from whom to seek help and expertise. The American Board of Neurology and Psychiatry (ABNP) has used for years ABNP (N) and ABNP (P) to designate "preference" in neurology and psychiatry, respectively. This will also make it easier for thoracic surgeons to avoid being called to do their less preferred parts of thoracic surgery and being uncomfortable with oneselves in doing something they know they are weak in. In addition, bright medical students will be less likely to view the general thoracic surgeons as a dying breed, but will see general thoracic surgery as a demanding specialty certified by the ABTS. (There is no need for me to elaborate that any surgery in the thorax is distinctive from general surgery.) I surely hate to see that down the pike the public, including our children, will have to suffer when their general thoracic surgical needs are relegated to an appendicial status.

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Reply

Your perspective as a long-established independent practitioner about the future of thoracic surgery training is very much appreciated. You have confirmed, from your viewpoint, some of the concerns expressed in the editorials that prompted your letter.

Your suggestion that ABTS certificates might be subdivided to identify individuals with special interest in cardiac or general thoracic surgery effectively would create certificates of special competence. It would not suffice to have either the training director or the diplomate state his or her special interest as the basis for granting a special interest suffix to the ABTS certificate. There would need to be criteria for granting special interest suffixes. The matter would require evaluating training programs as to their ability to provide subspecialty training, and it would otherwise become complex. One would need to be wary of the undesired and undeserved implication that diplomates should practice only in their area of special interest. The ABTS and the American Board of Surgery and many other specialty boards are very concerned about fragmentation of specialties. Great value is placed upon excellent *broad-based* training within specialties.

The editorials that prompted your letter, and the recent appointment by The Society of Thoracic Surgeons of an Ad Hoc Committee on Graduate Education under the chairmanship of Benson Wilcox, MD, signal that change in training requirements is under serious consideration. In keeping with the principles of your proposal, more formal recognition of subspecialization within thoracic surgery may be forthcoming. I believe that changes in the substance of training programs should be first, and that consideration of changes in certification *may* eventually follow.

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Cardiothoracic Surgery Training

To the Editor:

Having trained in the United Kingdom and South Africa, I have observed with interest the process of training in cardiothoracic surgery in the United States. I should like to add several points to the penetrating editorial by Peters [1] and the accompanying articles [2–6].

Most candidates for training as cardiothoracic surgeons interview and are awarded training posts while still in their third year of general training. This has twin effects: making it difficult to evaluate applicants and removing the incentive to strive for excellence once an appointment is secured.

On conclusion of formal general surgical training, the young surgeon takes the written component of his or her board examinations. While meeting the heavy clinical demands of the first year of cardiothoracic training, academic activity is understandably dominated by the impending oral examination in general surgery.

On completion of a recognized residency, the young surgeon will work while "board eligible." Although the board does not sanction the term, its widespread use, including in advertisements in the official journals of The Society of Thoracic Surgeons and the American Association for Thoracic Surgery, adds to the impression that board eligibility is a real entity and that successful completion of the examination is not a prerequisite for appointment as a cardiothoracic surgeon.

Mastering the basic principles of managing surgical patients and the elements of surgical technique does not take 5 years. However, the essential foundation must be acquired. Once the basic skills are instilled, time is devoted to training surgeons in the specific elements (technical and management) of complicated operations specific to the general surgical domain. It is this period that could be devoted more productively to an expanded program of cardiac and thoracic surgical instruction.

I suggest that among the proposed changes, strong consideration be given to adopting a program of several (3?) years of general surgical training culminating in an examination in the principles of surgery. This common basic training and the examination could usefully be made part of the program for all surgeons, including those who go on to specialize in general surgery.

The successful candidate may then commence cardiothoracic training, which should clearly be longer than the current 2 years. Near the end of the cardiothoracic training period, the candidate should face a written examination in all elements of cardiothoracic surgery—essay papers in addition to multiple-choice testing would improve evaluation of the candidates' process of reasoning and approach to specific problems.

The written component should be followed *within weeks* by oral examinations for all candidates whose performance on the written test is considered satisfactory. Certification by the Board should then be mandatory for appointment as a cardiac or thoracic surgeon.

I applaud your efforts to bring this vital issue to the attention of the profession.

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6. Benfield JR. What next in cardiothoracic training? Ann Thorac Surg 1991;51:820.

Reply

My colleagues and I appreciate your thoughtful letter about cardiothoracic training in the United States, expressed after your having completed training in the United Kingdom and in South Africa.

You suggest that general surgical training be shortened and that training in cardiothoracic surgery be extended. It certainly seems possible that such a change may occur, although there is a strong body of opinion that adheres to the need for complete training in general surgery and certification by the American Board of Surgery (ABS) as a prerequisite to examination by the American Board of Thoracic Surgeons (ABTS). During my relatively recent tenure as a director of the ABTS, the board confirmed that ABS certification was to be a prerequisite for examination. More recently, The Society of Thoracic Surgeons has appointed a committee under the chairmanship of Benson Wilcox, MD, to review training requirements in thoracic surgery. I feel certain that the issues addressed in our recent editorial symposium are also under discussion by ABTS and the Residency Review Committee in Thoracic Surgery. Thorough, healthy discussion that may lead to change is underway.

I do not think it realistic to expect that rapid ABTS certification upon completion of training can become the mechanism for granting privileges in thoracic surgery. The primary purpose of ABTS is to examine individuals who have completed approved training programs and to certify that successful candidates have passed the examination. The evaluation of training programs is the primary concern of the Residency Review Committee, which is an arm of the Accreditation Council for Graduate Medical Education. Privileges to practice cardiothoracic surgery are granted, as you know, by hospitals within which the practice takes place. I cannot foresee either sufficient shortening of the ABTS examination process or nationally uniform requirement for ABTS certification. I do believe that the leaders in thoracic surgery in the United States are ready to consider proposals for constructive change in cardiothoracic training.

Thank you for having taken the time to share your thoughts with us.

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Graduate Education in Thoracic Surgery

To the Editor:

Recently *The Annals* printed several articles [1–5] concerning the training of thoracic surgeons, instigated by the thoughtful questions raised by Richard Peters [6]. The August issue of *The Annals* included an editorial by Benson Wilcox [7] telling of his ad hoc committee, which is addressing this issue. Over the years, I have made some observations regarding this subject, some of which may be pertinent.

Many years ago, Eye, Ear, Nose, and Throat was one specialty. These surgeons did cataract surgery and Caldwell-Lucs. It became obvious that ophthalmology and otolaryngology were entirely different disciplines, and the two became separate specialties. I wonder if cardiac and noncardiac surgery have not also become "foreign" to one another.

Two discoveries led to a decline in general thoracic training—namely, coronary arteriography and flexible fiberoptic bronchoscopy. Coronary arteriography led to coronary artery bypass surgery. The huge numbers of these cases made cardiac surgery, by far, more dominant than general thoracic surgery in time spent in the operating room and in training. One got the impression that pulmonary surgery became the "country cousin" to coronary bypass surgery, and was done "between cases," at the end of the day or "whenever it can be worked in." Before coronary bypass surgery came into being, there was a pretty good balance between cardiac and noncardiac surgery in training programs. Now, however, it seems that many thoracic surgery training programs are producing essentially coronary artery surgeons. Residents are coming out of training highly skilled in coronary surgery, but many have never seen a segmental resection or a sleeve resection, and some even give the impression that hilar dissection is a mystery to them.

The second discovery, ie, the flexible bronchoscope, opened the field of bronchoscopy to almost anyone, removing the thoracic surgeon as the primary investigator of intrathoracic disease—especially tumors. Training programs may have been partially at fault as the staff was so busy getting all the coronary artery bypass procedures done each day that we lost by default to the pulmonary medicine people. Thoracic surgery residents today are inadequately trained in flexible bronchoscopy, and are entirely inept in the use of the rigid bronchoscope (still a necessary tool).

In conclusion, the old eye, ear, nose, and throat problem may be pertinent to the thoracic surgery enigma. Because cardiac surgery (especially coronary surgery) has become so demanding in time and effort, general thoracic surgery has taken a "back seat" in training programs. I sincerely believe that the diagnostic approach to intrathoracic pathology was done more expeditiously 10 (perhaps even 30) years ago than it is today.

It would seem to me that cardiac and noncardiac thoracic surgery should become separate training grounds after 1 year of training in both. The new techniques in thoracoscopy may give additional stimulus to general thoracic training. Hopefully, this modality will remain in the hands of surgeons.

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Neonatal Pneumonectomy

To the Editor:

I read with interest the recent article by Canver and associates [1], who described the successful management of a neonate with necrotizing bronchopneumonia secondary to pulmonary artery agenesis by right pneumonectomy.

I write this communication only to emphasize the need for ongoing close surveillance in this child because of the potential risk of serious tracheal obstruction secondary to compression by the aortic arch. The chest roentgenogram published in this article shows, 1 year after operation, serious mediastinal shift to the right with the entire cardiac silhouette in the right hemithorax. In the presence of a left aortic arch, this degree of mediastinal shift places substantial tension on the aortic arch, which is relatively immobile in its distal portion due to the attachments of the brachiocephalic branches and intercostal vessels.

I would like to bring to the attention of the readers an article published in this journal in 1978 [2] describing a technique that was successfully employed to manage this major complication of right pneumonectomy in the presence of a left aortic arch in the neonatal period.

Robert J. Szarnicki, MD

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1. Canver CC, Pigott JD, Mentzer RM Jr. Neonatal pneumonectomy for isolated unilateral pulmonary artery agenesis. Ann Thorac Surg 1991;52:294–5.
2. Szarnicki RJ, Maurseth K, de Leval M, Stark J. Tracheal compression by the aortic arch following right pneumonectomy in infancy. Ann Thorac Surg 1978;25:231–5.

Reply

To the Editor:

My colleagues and I appreciate Dr Szarnicki's interest in our report [1], and we agree with his appeal for the need of close surveillance of this child. Postpneumonectomy syndrome produces compression and malacia of the junction of the trachea and the main bronchus due to extreme mediastinal shift after right-sided pneumonectomy or left-sided pneumonectomy where a right-sided aortic arch is present. Correction is very complex but has been done, as in Dr Szarnicki's case [2], successfully in some patients.

In general, limited pulmonary resection that preserves all functioning lung tissue, ensuring maximal improvement, has been the procedure of choice in the pediatric population. Techniques and methods employed in the adult population to prevent complications of pulmonary resection, ie, cardiac herniation and airway compression, have not been employed in pediatric patients. Rare performance of pneumonectomy in the neonatal period may also explain the lack of published experience on this issue. However, in our case, life-threatening sepsis secondary to necrotizing pneumonia necessitated right pneumonectomy in the infant. Almost 2 years after the operation she remains healthy and growing normally.

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1. Canver CC, Pigott JD, Mentzer RM Jr. Neonatal pneumonectomy for isolated unilateral pulmonary artery agenesis. Ann Thorac Surg 1991;52:294–5.
2. Szarnicki RJ, Maurseth K, de Leval M, Stark J. Tracheal compression by the aortic arch following right pneumonectomy in infancy. Ann Thorac Surg 1978;25:231–5.

Acute Postinfarction Septal Rupture: Long-Term Results

To the Editor:

We enjoyed the paper by Loisance and colleagues [1] regarding short-term and long-term outcomes in patients receiving early surgical repair for acute postinfarction ventricular septal rupture. We also concur that the hospital mortality is quite high (45% in this report).

Without question, enhanced techniques of controlled ischemic myocardial reperfusion and improved methods of myocardial preservation delivery (antegrade and retrograde avenues) have increased our ability to assure patients' survival with this devastating complication. Nonetheless, there still remain patients who have insufficient residual myocardium for survival. The theoretical approach alluded to by Loisance and associates of emergency cardiac transplantation has been applied at Temple University Hospital.

In April 1986 a 57-year-old man was readmitted 3 days after discharge for a medically treated acute anteroseptal infarction

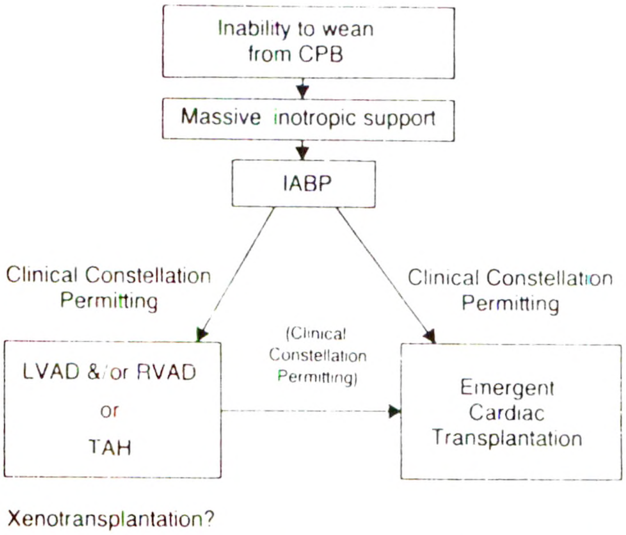
Inability to wean from CPB
Massive inotropic support
IABP
Clinical Constellation Permitting
Clinical Constellation Permitting
(Clinical Constellation Permitting)
LVAD &/or RVAD
or
TAH
Emergent Cardiac Transplantation
Xenotransplantation?

Fig 1. Treatment algorithm for postinfarction septal rupture with inability to wean from cardiopulmonary bypass (CPB). *(*IABP = *intraaortic balloon pump;* LVAD = *left ventricular assist device;* RVAD = *right ventricular assist device;* TAH = *total artificial heart.) (Reprinted from [2] by permission of Grune & Stratton, Inc.)*

with a previously determined ejection fraction of 0.16 before the acute ventricular septal defect. The patient was transferred to Temple University Hospital in shock with an intraaortic balloon pump. Standard reparative technique was performed, but the patient could not be weaned from cardiopulmonary bypass. The family was made aware that a "long shot" to rescue the patient would be an emergently orchestrated orthotopic heart transplantation with a procurement process initiated while the patient was on cardiopulmonary bypass. Fortunately, a heart was available. The patient was maintained on cardiopulmonary bypass for more than 11 hours and fully recovered after the transplantation. He remains alive and well today and works as a physicist/engineer who continues to be granted patents for his new ideas; he also plays competitive tennis in a local league.

Figure 1 summarizes our treatment algorithm for this clinical problem.

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A Lymphoid Tumor Obstructing the Trachea in a Child

To the Editor:

We have read with interest the reports of lipoma and malignant fibrous histiocytoma of the trachea presented in *The Annals* [1, 2] and want to add a personal experience reflecting on the potential life-threatening presentation of these lesions.

A 5-year-old girl was seen at our hospital in February 1987 with severe shortness of breath mimicking "laryngeal croup." She had been given medical treatment at another hospital for 3 days and then referred to us owing to severe dyspnea and a worsening clinical picture. During the evaluation in the emergency room the posteroanterior chest roentgenogram showed an intratracheal shadow about 0.5 cm at the level of carina. Bronchoscopic examination under general anesthesia showed an obstructing polypoid lesion protruding into the lumen just above the level of tracheal bifurcation. The mass bled easily and had a soft, glistening yellow appearance.

The vital findings returned to normal upon endoscopic removal of the mass. The tissue fragments were 1.5 × 1 cm in aggregate, and the microscopic sections revealed a cellular tumor with prominent vascularity. The cells were large and pleomorphic with occasional binuclear and mitotic figures (Fig 1). The cytoplasm was negative for myoglobin and desmin, positive for periodic acid-Schiff reaction, and negative for S-100 protein and keratin, whereas positivity was observed for lysozyme and epithelial membrane antigen.

The systemic work-up of the patient did not reveal any hematological and lymphoid abnormality, and a malignant—at least locally—histiocytic tumor was considered. The patient was given a chemotherapeutic regimen of vincristine, 2 mg/m^2 intravenously; cyclophosphamide, 2.5 mg/kg orally; and Dactinomycin, 0.015 mg/kg intravenously, in combination two times at a 1-month interval. Although the patient was reported to be in good health, until recently she was not brought to periodic controls.

A recent reevaluation of the lesion found it to be compatible with the so-called Ki-1 lymphomas, which are said to possess discernible histological appearances akin to ours [3, 4]. A Ki-1 stain on a previously stained reticulin—as the paraffin block was not available—showed a fairly convincing staining supporting this diagnosis (Kozakewich H; personal communication).

(We greatly appreciate the kindness of the late Dr Vawter [Northwestern, 1948] and Dr Kozakewich who accepted our

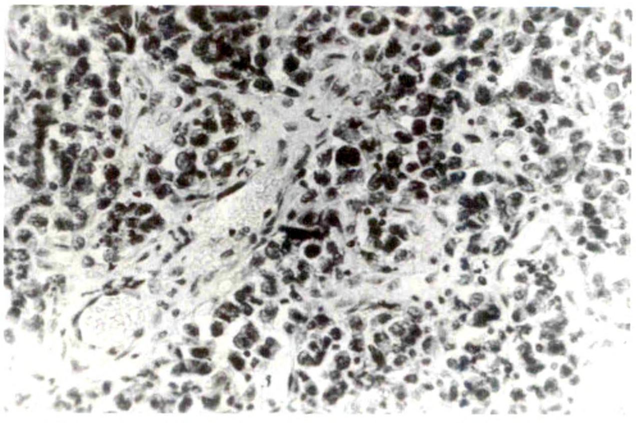

Fig 1. Microscopic intermediate-power view of the lesion showing vascularity and prominent tumor cells. (Hematoxylin and eosin.)

consultation regarding this peculiar case. This case was opened for discussion at the meeting of Turkish Pathologists in November 1990 during the 9th National Congress.)

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The Role of Neck Dissection in Thoracic Esophageal Cancer

To the Editor:

Kato and associates [1] from the Japanese National Cancer Center recently published their results of a randomized study on the efficacy of the addition of bilateral cervical lymph node dissections for thoracic esophageal carcinoma. They concluded that the addition of neck dissections to their standard of esophagectomy and mediastinal and abdominal lymph node dissections resulted in a statistically significant increase in 5-year survival. An accompanying editorial by D. B. Skinner [2] of Cornell Medical Center was cautious in accepting the results because of the small numbers of patients in each group (77 and 73) but believed that further randomized studies should test the procedure and accepted the results as presented by Kato and associates.

A careful review of the report shows that Kato and associates may have reached an invalid conclusion. In this study 73 patients in group B were randomized to receive esophagectomy and mediastinal and abdominal lymph node dissections. Seventy-seven patients in group A received this operation and additionally had bilateral cervical lymph node dissections. Separate teams of surgeons were assigned to operate on group A and group B. It was stated that the two teams of surgeons were of equivalent skill. The patients in group B were significantly older than those in group A, and although the difference was not statistically significant, a higher proportion of patients in group B had T3 or T4 tumors (47% versus 40%), had N1 rather than N0 nodes (63% versus 56%), and were in stage III or IV rather than I or II (56% versus 47%). Thus the patients in group B were older and had more advanced disease. Patients were accrued from December 1985 to December 1989, and the report was accepted for publication in December 1990. Thus, although a median follow-up is not given, it is probably less than 3 years. Using a life-table method they predicted their 5-year survival in group A was 48.7% versus 33.7% for group B ($p < 0.05$).

Despite the lesser operation performed on group B and the equivalent skill of the surgeons, the operative (30-day) mortality rate of group A was 2.6% versus 12.3% in group B. Operative deaths were not censored in their survival calculations. If the 5-year survivals calculated by the life-table analysis are assumed to reflect the survivals that would be obtained after 5 years of follow-up, then eliminating the operative deaths from the survival calculations results in 5-year survivals of 49% and 39% for the two groups. Further, because the life-table analysis projects forward the poor early survival due to the operative mortality in group B, the projected 5-year survival will underestimate the true 5-year survival, and the actual difference in survival at 5 years of follow-up may be smaller than predicted. In fact, there is only a small difference in deaths due to disease between the two groups (groups A and B, 18 and 21, respectively). In addition to the unequal deaths due to operative mortality, group A had only 7 patients die of "other" causes whereas group B had 12. Therefore 50% of the deaths in group A were disease-related but only 33% of the deaths in group B were due to disease. The disease-specific survivals for groups A and B are 56% and 48%, respectively ($p > 0.15$ by χ^2). The statistically significant overall survival advantage is largely due to this difference in non–disease-related deaths. It is unlikely that the less involved procedure performed on group B caused the higher mortality in that group. More likely, either an unaccounted-for imbalance in the patients, as represented by the significantly higher age of group B, or the unequal skill of the surgeons, as suggested by the higher overall and fatal complication rates in group B, caused the discrepancy. Rather than the enhanced survival being due to the neck dissections, more probably the design and execution of this trial were flawed.

The accompanying editorial suggests that further randomized trials on this question may be warranted. The lack of efficacy in this trial, as shown in our reanalysis of their results, suggests it would be imprudent to subject patients to the possible morbidity of the bilateral neck dissection without clearer evidence of therapeutic advantage. Until a more complete analysis of the long-term results of this trial is available, we believe further studies on the efficacy of neck dissections should not be attempted.

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1. Kato H, Watanabe H, Tachimori Y, Iizuka T. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg 1991;51:931–5.
2. Skinner DB. Cervical lymph node dissection for thoracic esophageal cancer. Ann Thorac Surg 1991;51:884–5.

Reply

To the Editor:

Berk and Coia from Pennsylvania question our conclusion that the addition of neck dissections to our standard esophagectomy with mediastinal and abdominal lymph adenectomy for thoracic esophageal carcinoma resulted in a significant increase in survival [1]. They surmise that the difference in the survivals in the two groups resulted from (1) the higher age of group B, (2) more advanced disease in group B, (3) higher overall and fatal complication rates in group B, or (4) the unequal skill of surgeons.

We have performed additional analyses using the life-table method, log-rank test, and generalized Wilcoxon method in regard to the issues proposed by them, with the following results.

(1) As written in our report, after patients older than 75 years or patients who died of operative causes are excluded, the two survival curves remain significantly different ($p < 0.05$). The 5-year survival rates for patients equal to or younger than 75 years in groups A ($n = 71$) and B ($n = 62$) are 46.4% and 33.6%, respectively. Their average ages are 59.1 years in group A and 61.6 years in group B, and the difference is not significant.

(2) As written in our report, after stratification by tumor stage, group A showed significantly better survival rates in stage III ($p < 0.05$) and stage IV ($p < 0.01$). The 5-year survival rate for pT3 patients in groups A ($n = 32$) and B ($n = 33$) are 39.9% and 20.2%, respectively, and the difference is significant ($p < 0.05$). After T4 patients are excluded, the 5-year survival rates for groups A and B are 49.5% and 31.1%, respectively, and the two survival curves remain significantly different ($p < 0.01$). After stage IV patients are excluded, the 5-year survival rate in group A is 55.0% versus 40.7% in group B, and the difference of the two survival curves is significant ($p < 0.01$).

(3) When deaths caused by operative complications and other diseases are censored in the calculation, the 5-year survival rates in groups A and B are 56.8% and 39.1%, respectively. The difference in the two survival curves is significant ($p < 0.05$). Finally, when patients with advanced disease (pT3 and pT4) and younger than 75 years in each group are compared, censoring deaths related to operation or to other diseases, the 4-year survival rates for groups A and B are 39.3% and 21.2%, respectively, and the difference between the two survival curves is statistically significant ($p < 0.05$). That suggests the efficacy of neck dissection in the prognosis of advanced disease.

All these results show that the difference in survival of the two groups is due to neither the difference in non–disease-related death nor imbalance in the patients' age or tumor stage, and again confirm a positive effect of neck dissection for thoracic esophageal carcinoma especially for advanced disease, even if imbalance in the patients does exist between the two groups as indicated by Berk and Coia.

(4) The remaining issue of our study may originate in the inequality of surgeons between the two groups. We cannot make further comment about Berk and Coia's suspicion of inequality, although we believe that there is not such a large inequality of skill that it would influence the patients' prognosis.

Berk and Coia's warning of possible morbidity as an argument against neck dissection seems inadequate. The operative mortality in group A was 2.6%, which seems to be acceptable when compared with the results in the world literature [2]. As we showed in the report, the only complication in 77 cases of neck lymph node dissection was one case of unilateral vocal cord palsy by which the patient suffered only hoarseness. When a patient gets his or her life in exchange for hoarseness, the exchange must be considered profitable. Furthermore; the 4-year survival rate of 47.9% for 20 patients with positive neck lymph nodes in group A strongly suggests a great benefit of additional neck dissection, because the majority of the patients would not have survived without dissection of the positive cervical nodes.

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Southern Thoracic Surgical Association Rules for Submission of Abstracts

Abstracts for papers to be presented for the 1992 Annual Meeting are now being accepted. The deadline for postmark of abstracts is May 15, 1992. An original and one copy should be submitted, using the official Association abstract form, to Walter H. Merrill, MD, Chairman, Program Committee, the Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Additional forms are available upon request from the Association.

Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. *Abstracts received after the deadline will not be considered.* The information requested at the bottom of this form must be completed indicating who is to receive the notice of acceptance or rejection and who will present the paper if accepted.

Abstracts may be submitted for the regular program, the Forum, or either. Papers selected for the Forum will be published in *The Annals of Thoracic Surgery* if they pass the usual editorial review.

Essayists are reminded that all papers accepted for presentation must be submitted in triplicate to Hendrick B. Barner, MD, Secretary-Treasurer, at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation.

Abstracts frequently obscure the value of their content because they are poorly organized. It is important that methods and results be clearly defined in the abstract; general statements such as ''results will be presented'' are not acceptable. When a procedure or method is stated to have ''advantages,'' those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Presentations in the regular program are limited to 10 minutes; those in the Forum are limited to 5 minutes.

In discussion of papers, the Association encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of the discussion in the form of ''secondary papers'' will not be welcomed.

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1. Title of abstract must be completely CAPITALIZED.
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Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ General Thoracic Surgery, Las Vegas, Nevada—April 2–3, 1992

This postgraduate course is sponsored by the American College of Chest Physicians and the University of Nevada School of Medicine. For information, contact ACCP, Division of Education, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Twelfth Annual Meeting of the International Society for Heart Transplantation, San Diego, California—April 2–4, 1992

For information on this meeting, contact ISHT, 435 N Michigan Ave, Suite 1717, Chicago, IL 60611; or telephone (312) 644-0828.

■ One Hundred Twelfth Annual Meeting of the American Surgical Association, Palm Desert, California—April 6–8, 1992

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Forty-first Annual Meeting of the American College of Cardiology, Dallas, Texas—April 12–16, 1992

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ Seventy-second Annual Meeting of the American Association for Thoracic Surgery, Los Angeles, California—April 27–29, 1992

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526–4018).

■ Thirty-eighth Annual Meeting of the American Society for Artificial Internal Organs, Nashville, Tennessee—May 7–9, 1992

For information on this meeting, contact ASAIO Registration, 2200 North Federal Highway, Suite 201, Boca Raton, FL 33431-7710.

■ Fourteenth World Congress of The International Society for Heart Research, Kobe, Japan—May 10–14, 1992

For information on this meeting, contact Makoto Nagano, MD, Secretariat, XIV World Congress of ISHR, Department of Internal Medicine, Jikel University Medical School, Aoto Hospital, 6-41-2 Aoto, Katsushika-ku, Tokyo 125, Japan.

■ The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Chicago, Illinois—June 8–10, 1992

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Cardiostim 92, Nice, France—June 17–20, 1992

For information on this meeting, contact Dr J. Mugica, Centre Chirurgical Val d'Or, 16, rue Pasteur, 92211 St-Cloud Cedex, France; or telephone (33) 1.46.02.70.72 (facsimile: (33) 1.46.02.05.09).

■ Eighteenth Annual Meeting of The Western Thoracic Surgical Association, Kauai, Hawaii—June 25–27, 1992

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Forty-first International Congress of the European Society for Cardiovascular Surgery, Montpellier, France—September 6–9, 1992

For information on this meeting, contact ESCVS Congress 92, Le Corum, BP 2200-F 34027, Montpellier Cedex 1, France; or telephone (33) 67.61.67.61 (facsimile: (33) 67.61.67.00).

■ Sixth Annual Meeting of The European Association for Cardio-Thoracic Surgery, Geneva, Switzerland—September 14–16, 1992

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■ First International Meeting of Thoracic Surgery, Barcelona, Spain—October 9–10, 1992

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■ American College of Surgeons, New Orleans, Louisiana—October 11–16, 1992

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Concepts in Myocardial Revascularisation, Leicester, United Kingdom—October 15–16, 1992

For information on this international symposium, contact Mrs Fiona Legate, Department of Cardiology, Glenfield General Hospital, Groby Rd, Leicester, UK; or telephone (44) 533-871471, ext 3038 (facsimile: (44) 533-875792).

■ Fifty-eighth Annual Scientific Assembly, American College of Chest Physicians, Chicago, Illinois—October 26–30, 1992

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association, Wesley Chapel (near Tampa), Florida—November 5–7, 1992

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ Sixty-fifth Scientific Session of the American Heart Association, New Orleans, Louisiana—November 16–19, 1992

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ Twenty-ninth Annual Meeting of The Society of Thoracic Surgeons, San Antonio, Texas—January 25–27, 1992

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

■ Third World Congress of the International Society of Cardio-Thoracic Surgeons, Salzburg, Austria—January 25–27, 1993

For information on this meeting, contact Prof Dr Felix Unger, c/o Interconvention, Austria Center Vienna, A-1450 Vienna, Austria; or telephone +43/1/23 69-26 43 (facsimile: +43/1/23 69-648).

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SITUATIONS AVAILABLE

Thoracic/vascular surgeon needed to join prominent, active 3-man group in desirable suburban community in greater NY metropolitan area. Excellent opportunity for well-trained, highly motivated individual. Recent graduate preferred. Possible academic affiliation. Please respond with CV.

Please respond to Box 404. 404I/C

Cardiothoracic and vascular surgeon, board eligible or certified, to join 2-man private practice in Ft. Lauderdale, Florida. Send CV.

Please respond to Box 542. 542L/E

Cardiothoracic surgeon, BE/BC, to join busy 1-man private practice in mid-Michigan. Excellent opportunity. Salary leading to partnership. Please send CV and references.

Please respond to Box 601. 601J/C

Cardiovascular and thoracic surgeon, board certified or board eligible, to join a rapidly expanding single hospital practice in the upper Midwest. Salary leading to partnership. Please respond with curriculum vitae.

Please respond to Box 609. 609J/C

Private practice opportunity in New York. Adult and pediatric cardiac surgery only. Postgraduate training in pediatrics a plus but will seriously consider all qualified applicants. Please respond with CV.

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Excellent practice opportunity for well-mannered, technically accomplished CV surgeon in California wine country. Growing 2-surgeon practice in beautiful semirural area close to San Francisco—great family environment. Prefer young surgeon with 2–5 years' experience, ABTS board certified.

Please respond to Box 621. 621J/C

Cardiothoracic surgeon, BE/BC, wanted to join established practice in mid-Michigan group of two. Ninety percent of practice is adult surgery and ten percent is general thoracic surgery. Respond with CV and names of references.

Please respond to Box 644. 644L/E

The Division of Thoracic and Cardiovascular Surgery at the University of New Mexico School of Medicine in Albuquerque is seeking applications for a full-time faculty position at the Assistant Professor level for July 1992. We are looking for an individual with excellent surgical skills, strong interest in research and teaching. The candidate must be board eligible or certified. We offer a competitive salary. This is an excellent opportunity for an individual interested in academic achievements as well as a good clinical experience.

Please forward curriculum vitae and three letters of recommendation to Jorge A. Wernly, MD, Chief, Division of Thoracic and Cardiovascular Surgery, University of New Mexico Medical Center-ACC2, Albuquerque, NM 87131. An affirmative action/equal opportunity employer. 646L/C

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Please respond to Box 648. 648L/E

Cardiovascular and thoracic surgeon—board eligible/certified to join a noncardiac surgical practice located in the mid-Atlantic states. Respond with CV and details of experience. Recent graduate preferred.

Please respond to Box 654. 654A/C

Cardiothoracic surgeon, BC/BE, wanted to join adult cardiac surgery program in the South. Solo practice is very busy serving as regional referral center. First-rate medical facilities, liberal compensation package, and warm hospitality await you! Please send CV.

Please respond to Box 656. 656A/C

Cardiovascular and thoracic surgeon, BC/BE, to join a three-man established expanding private practice in central Florida. Excellent salary and fringe benefits package leading to partnership.

Please respond with CV to Wayne McGraw, PO Box 3130, Ocala, FL 32678; (904) 867-8311. 665B/D

Cardiothoracic and vascular surgeon, BE/BC, wanted to join a busy, well-established practice in Amarillo, Texas. Recent graduate preferred.

Please send CV to Henry E. Martinez, MD, 1901 Medi Park, Suite 1050, Amarillo, TX 79106; (806) 358-5108. 666B/G

Thoracic surgery: busy practice, mostly pulmonary and esophageal surgery and pacemakers in medium northeast city; two large hospitals; no pump, vascular, or general surgery. Financial arrangements appropriate for experienced surgeon available. Please respond with CV.

Please respond to Box 668. 668B/C

Thoracic/cardiovascular surgeon: three-man group in suburban New York doing general thoracic and peripheral vascular surgery desires new graduate of approved thoracic program with training in vascular surgery. Please respond with CV.

Please respond to Box 671. 671C/E

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Please respond to Box 672. 672C/F

Cardiovascular surgeon: excellent practice opportunity for recently trained BC/BE to join a two-man busy practice in San Diego, California. Salary leading to full partnership. Please send curriculum vitae.

Please respond to Box 673. 673C

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Send CV and references to PO Box 1295, Philadelphia, PA 19105. 674C/E

Cardiovascular, thoracic surgeon with vascular experience needed to join solo practioner. Must be board certified. Must be interested in people, personable, and interested in doing a good job. Excellent salary and benefits for the right candidate. Preferable with several years practice experience.

Please respond to Box 675. 675C

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Please respond to Box 678. 678C

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Direct Inquiries with current vita to Gordon F. Murray, MD, Professor and Chairman, Department of Surgery, WVU Health Sciences Center, Morgantown, WV 26506. West Virginia University is an equal opportunity/affirmative action employer. 679C

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Please respond to Box 676. 676C/D

FELLOWSHIPS

Fellowship in vascular surgery—The Deborah Heart and Lung Center is currently seeking qualified applicants for a Vascular Fellow position.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 651A/C

Surgical residents/fellows—clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 653A/C

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Hovald K. Helseth, M.D., Chief
Division of Cardiothoracic Surgery
Department of Surgery
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100 Broad Street
Glens Falls, NY 12801

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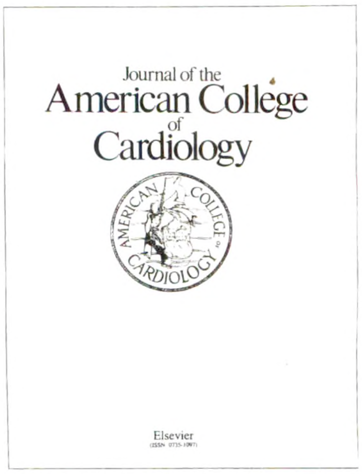

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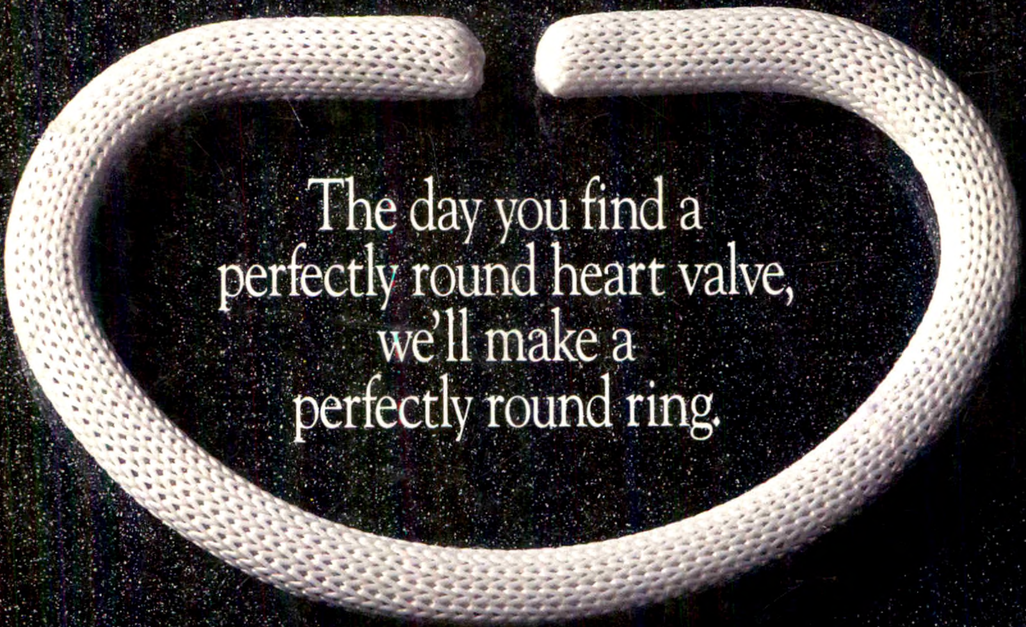

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